Acta Genetica et Statistica Medica

Vol. IV 1953 No. 4

INDEX

BASEL (Switzerland) S. KARGER NEW YORK

Printed in Switzerland

"*Acta Genetica et Statistica Medica*" is issued quarterly. Each issue has approximately 96 pages. The annual subscription rate is Swiss frs. 48.—.

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«*Acta Genetica et Statistica Medica*» paraît en fascicules trimestriels d'environ 96 pages. Le prix de l'abonnement annuel est de frs. suisses 48.—.

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«*Acta Genetica et Statistica Medica*» erscheint vierteljährlich in Heften von etwa 96 Seiten zum Jahresabonnementspreis von sFr. 48.—.

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Böök, J. A.: Acta genet. 4, 345–414, 1953

From the State Institute for Human Genetics, Uppsala, Sweden
Head: Professor Gunnar Dahlberg, M.D., LL.D.

A GENETIC AND NEUROPSYCHIATRIC INVESTIGATION OF A NORTH-SWEDISH POPULATION

With special regard to schizophrenia and mental deficiency

PART II.

MENTAL DEFICIENCY AND CONVULSIVE DISORDERS

By J. A. BÖÖK

CONTENT

INTRODUCTION

The present paper is a continuation and the final part of a genetic and neuropsychiatric investigation of a North-Swedish population. The investigation area, which had the character of a geographic isolate, consisted of the parishes of Pajala, Junosuando and Muonionalusta in Sweden. The population in 1949, at the end of the field work, totalled a population of 8,981.

The character of the investigation area and the methods which were used in collecting the data were described in part I of this report, which was published in Vol. 4:(1):1–100 of this Journal. Furthermore, this first part of the report contained the results in regard to the investigations on psychoses. A short paper entitled "Schizophrenia as a Gene Mutation", which appeared in Vol. 4:(2–3): 133–139 of this Journal, was also based on data obtained from this population.

In this paper, the findings in regard to mental deficiency and convulsive disorders will be reported. The bibliography and a summary of the total investigation will also be given in this paper. A limited number of typewritten copies of the case histories which have been evaluated in this paper, as well as those evaluated in part I of this work, will be made available for qualified research workers through the Swedish State Institute for Human Genetics, Uppsala, Sweden.

CHAPTER I.
MENTAL DEFICIENCY

In a recent paper (*Böök* [1953b]), I have tried to give a synopsis of the present status of research concerning mental deficiency (*syn. oligophrenia*) with special regard to its genetic aspects. A comprehensive paper on the same topic was read by *Fraser Roberts* at the International Congress of Psychiatry in Paris in 1950 (*Fraser Roberts* [1950]). It should be noted, however, that in conformity with Scandinavian psychiatry I preferred to restrict the use of the

term oligophrenia to those individuals who are unable to attend ordinary schools even if instructions are given in special classes. This would mean a dividing line at *roughly* an IQ of 60–70 (cf. also *Dahlberg* [1951]). *Fraser Roberts*'s concept is wider and includes those mentally retarded or borderline individuals who could be regarded as belonging to the minus-tail of the normal curve of IQ-test responses. All presently used types of classification into groups, based either on IQ tests or social performance, are, of course, arbitrary. In this paper, the term oligophrenia will be used in the restricted sense indicated above, and other types of mental retardation will be left out of consideration.

It should be clear that oligophrenia is a sociologic and psychologic concept. It refers to a certain type of human behaviour which may have any yet unknown number of causes. Etiologic research, therefore, has to analyse the composition of a group of individuals who happen to have some rather peripheral symptoms in common and, with the aid of available tools of medicine and biology, try to identifiy specific entities. A significant number of such attempts has been made, and by now a number of specific pathogenetic entities are recognized. Some of these are almost exclusively environmental, other almost exclusively genetic. For details the reader is referred to *Böök* [1953 b] and to the monographs by *Penrose* [1949] and *Tredgold* [1949]. Such specific entities with known or partly-known genetic factors are instrumental as a primary cause (e.g., *Smith* etiology, however, still comprise a minority of all oligophrenics. Some 50–80 per cent still have to be referred to as "undifferentiated oligophrenia of unknown etiology". The accumulated familial data of representative series of this latter category appear to show that genetic factors are instrumental as a primary cause (e.g., *Smith* [1929], *Penrose* [1938], *Juda* [1939] and others). However, the hypothesis that this category constitutes a genetic entity as advanced by *Brugger* [e.g., 1941] has not been sufficiently supported by facts. Although at present such an hypothesis cannot be disproven on account of lack of crucial data, it seems, on *a priori* grounds, unlikely. Relatively recently, phenylketonuria (*Fölling* [1934], *Jervis* [1939]) was separated from this group as a specific clinical and genetic entity by means of biochemical studies. It does not appear likely that this would have been the only special type hidden in the undifferentiated group. At any rate, until more data have accumulated on the pathology behind the peripheral symptom "oligophrenia",

discussions about the more detailed genetic background seem premature. In view of the few facts available as yet, and stressing the secondary nature of the mental retardation insofar as etiologic research is concerned, I have proposed the following tentative classification:

1. Genetic diseases or defects which invariably cause impaired brain function, apparent as mental defect. This group would include clinically, pathologically or biochemically differentiated as well as still undifferentiated types.

2. Genetic diseases and defects with mental defect as an occasional symptom.

3. Environmental group in which mental defect occurs as a symptom caused by physical lesions of all kinds (e.g. brain injuries, infectious diseases, intoxications) or adverse psychic mechanisms.

SURVEY OF THE TOTAL OLIGOPHRENIC MATERIAL

The main procedures which were followed in the ascertainment of the data and the definition and classification of the *propositi* were described in part I of this report (*Böök* [1953 c] p. 17–25). However, a few other pertinent details should be mentioned or emphasized here.

As in the case of the work on schizophrenia the main purpose of the registration of all available data on oligophrenia for the period of 1902–1949 (i.e. inclusive of those who had died or emigrated) was to secure the best possible ascertainment of all oligophrenics who were living and residents of the investigation area on the cross-section date. Similarly, those registered as *propositi* for the total period are *primary propositi*. It should be noted that for the genetic analyses the definition of a *propositus* was changed to comprise only an individual who was living and resident on the cross-section date.

In view of the anticipated heterogeneity of the oligophrenic material, it was decided to attempt to divide the oligophrenics into different groups by means of clinical or other non-genetic criteria and then to analyse these groups separately. Psychologic or other criteria referable to the intelligence status of the individuals were *not* used for differentiation, nor was the presence or absence of convulsive disorders used to refer a case to a particular group.

This grouping was intended to be merely a method of exploring by trial and error among the oligophrenics of this population to see if there would be some who could be referred to special clinical and/or genetic entities.

Diagnosis.

The principles on which the diagnosis of oligophrenia was based were mentioned previously (cf. *Böök* [1953 c] p. 35). Reservations must, of course, be made concerning some individuals who had died or emigrated by September 1, 1949. In table 7 (*Böök* [1953 c]) there are 44 individuals, labelled as "idiocy or imbecility of unknown etiology". For 8 of these, the only available information was their registration in the parish register as mental defectives (4 males and 4 females). Two further females were included on the basis of information obtained from relatives or other informants. For 3 males and 1 female, all appearing in the parish register, additional information was obtained from relatives. All other cases had been professionally examined either by district physicians or physicians at mental institutions.

Of the above-mentioned 44 cases, only 5 have been utilized in the following analysis, notably then as secondary cases in the genetic calculations.

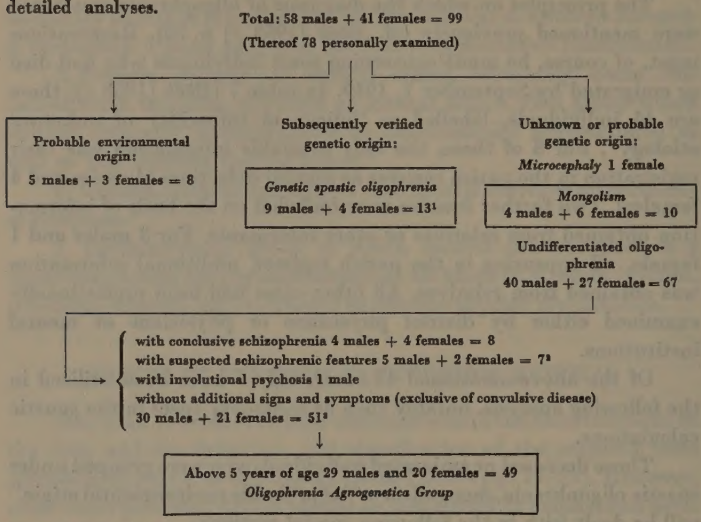
Those deceased or emigrated individuals who were grouped under spastic oligophrenia, mongolism or "of probable environmental origin" will be dealt with in the following special sections.

The cross-sectional propositi.

On September 1, 1949, a total of 99 oligophrenic individuals were registered. Their explorative grouping is indicated in table 1. With the limitations of methods of examination that can hardly be avoided in a field study, it is, of course, no surprise that most of the cases remained undifferentiated.

First, those oligophrenics who could be referred to a probable environmental origin were sorted out. Then 3 types were differentiated on the basis of physical or neurologic characteristics. These were the well-known mongoloid idiots, one single microcephalic idiot and, perhaps most interesting, no less than 13 cases with cerebral diplegia (later named genetic spastic oligophrenia). Finally, by a number of exclusions as shown in table 1, we obtained a group of 49 individuals who did not display any specific or consistent physical or mental characteristic. The reason for abstaining from using convulsive disorders as a differential sign was that all kinds of seizures are relatively common, especially in low grade oligophrenics. It therefore seems questionable if such convulsive disorders represent any-

Table 1. Survey of the explorative grouping of the oligophrenic individuals living and resident on September 1, 1949. The encircled groups were subjected to more detailed analyses.



[1] Thereof 1 male with convulsive disease. [2] Thereof 1 male and 1 female with convulsive disease. [3] Thereof 4 males and 4 females with convulsive disease.

thing but a consequence of the generally impaired function of the oligophrenic brain. This final group, which is relatively homogeneous insofar as symptomatology is concerned, was called oligophrenia agnogenetica. This name, of course, has no meaning other than to signify how the group was composed and that the etiology was unknown. It should, perhaps, be added that for 45 cases a positive statement was obtained as to the congenital nature of the defect and for the remainder this etiology was probable.

In connection with the exclusion from the explorative groups of 7 oligophrenics with suspected schizophrenic features, some comments should be made on the diagnosis of schizophrenia in oligophrenics or *vice versa*. I shall not enter into the question of whether or not there are biologic connections between these two, a possibility that has been rejected, apparently on good grounds, by *Kallmann* and co-workers [1941]. Instead, I want to emphasize some diagnostic difficulties which are especially pronounced in studies like the present one. If a reliable history of infancy and childhood is not available and the diagnosis has to be based exclusively on clinical

observations for a couple of hours in the patient's home, it might be entirely impossible to make a differential diagnosis between oligophrenia and schizophrenic simple dementia in an adult. Furthermore, some individuals who are undoubtedly oligophrenic may display abnormalities of behaviour resembling schizophrenia. Only through extended observation could it be possible to disclose or, at any rate, to evaluate such symptoms. These are all inefficiencies that are inherent in any field study. On the other hand, under similar circumstances, the diagnosis of oligophrenia in an individual who displays all the classical signs of schizophrenia might be rather tricky. When examining the files of those schizophrenics of the present data who had been hospitalized, I found a few instances in which a patient had been a chronic schizophrenic for 5 to 10 years before admission but, on account of psychologic tests or general behaviour, was diagnosed as an imbecile when entering the hospital. Unless additional information could be obtained to the effect that the patient had been oligophrenic prior to the onset of schizophrenia, such diagnoses were not accepted. After revision, there remained 4 males and 4 females who, with reasonable certainty, represented true schizophrenic psychoses in oligophrenics (all imbeciles).

Those 5 males and 2 females who displayed some schizophrenic features were all imbeciles. They were excluded from the oligophrenia agnogenetica group to obtain a symptomatologically homogeneous category. Their suspected schizophrenic signs were not of a quality to justify even a questionable diagnosis of schizophrenia according to the criteria used in this study. They have thus been evaluated only as oligophrenics. One of these cases is presented here as an example.

15/49. K.E.J., male, born 1919. According to his father and school-teacher, he had been mentally retarded since childhood. He learned to read and write but could hardly follow other instructions. In 1931 he was diagnosed as an imbecile by the district physician and recorded in the parish register. He was described as having an irritable and explosive temperament. In 1945 he had an accident while working (no head injury). After that he showed odd behaviour, talked to himself, went out to the forest and said he was going to do away with himself. Sometimes he stayed in bed for several days and refused to work. His father said that the patient had stayed in bed for two years. Later on he improved but avoided people and did not want to go to the village. Examined in 1949 (*Böök*): "He had obvious difficulties in grasping the questions and his reasoning appeared rather primitive. Could not perform simple multiplications. However, he could count and knew the different coins and bills as well as the hours and minutes of a watch. My impression was that his intellectual development corresponded to that of a child of 9–10 years of age. His attitude to the examination was one of apparent suspicion. He was well

oriented and his memory showed no apparent deviations from what to be expected with regard to his intellectual development. He seemed rather preoccupied and revealed no emotions. A normal personal contact could not be established; it was as if the call did not interest him. He denied all gross psychopathologic symptoms such as hallucinations, ideas of persecution and so forth. He could not, or did not want to, explain why he sometimes stayed in bed without being ill. – His physical examination was negative. – Diagnosis: Oligophrenia (with suspected schizophrenic features)."

Table 2. Oligophrenia. All cross-sectional *propositi* (99). Type of ascertainment.

Category	First registration through:					Total
	Parish records	Mental hospital	Mental asylum	Welfare organization	Field work	
Probable environmental origin . .	7				1	8
Genetic spastic oligophrenia . .	10				3	13
Oligophrenia agnogenetica group .	37	1	1	2	10	51
Mongolism . . .	4				6	10
Others	15				2	17
Totals	73	1	1	2	22	99

Type of ascertainment.

Table 2 shows how the oligophrenic *propositi* were first registered. The majority (73) were known to the local authorities, but no less than 26 had not been registered at the vicars' offices and, of these latter individuals 22 were revealed during the field work. It should be mentioned, however, that 8 of the screening *propositi* were below school age (7 years). *Age and sex distribution* is shown in table 3.

Degree of mental defect.

To give the reader an approximate idea of the distribution of the *propositi* on different degrees of intellectual impairment, they have been referred to 4 categories in table 4. As emphasized in the text of this table, the divisions have been based on clinical, psychological and sociological grounds. It is probable that I have included a few more cases of high grade oligophrenia in my data than *Sjögren* [1948] did in his West Swedish study. *Sjögren* emphasized that he included only idiocy and *severe* imbecility. On the other hand, he wrote that all individuals who were recorded in the parish registers

Table 3. Survey of age distribution of all cases of oligophrenia (58 males and 41 females) living and resident in the investigation area on September 1, 1949, by exploration groups. Mean age for females 25.1 and for males 28.8 years.

Age	Oligophrenia agnogenetica		Undiff. oligophrenia + schizophrenia		Undiff. oligophrenia with schizophrenic features		Genetic spastic oligophrenia		Mongolism		Oligophrenia of probable environmental origin		Total
	M	F	M	F	M	F	M	F	M	F	M	F	
0– 4	1	1					1			2		1	6
5– 9	1	3						2	3	3			12
10–14	7	4					2	1	1				15
15–19	3	3					2			1	1		10
20–24	3						1					1	5
25–29	6	1[1]	1		1			1			2		12
30–34	1	1			2								4
35–39	1	4		2	1		2					1	11
40–44	2	1	1			2	1				1		8
45–49		1											1
50–54	1	3	1	1	1						1		8
55–59	2												2
60–64	1		2[2]										3
65–69	1			1									2
Totals	30	22	5	4	5	2	9	4	4	6	5	3	99

[1] Microcephaly. [2] One case not schizophrenia but involutional psychosis.

Table 4. Oligophrenia. All cross-sectional *propositi*. Clinical evaluation of the intellectual development of 99 cases. The IQ limits are given only to give an approximate idea of the present author's conception of the grouping, and they do not refer to psychometric tests. Individuals registered in the parish records are given within brackets.

Category	Low grade idiots (IQ 0–20)	Idiots (IQ 20–35)	Low grade imbeciles (IQ 35–55)	Imbeciles (IQ 55–70)	Total
Prob. environmental origin	2	1	3	2	8
Genetic spastic oligophrenia	8	1	4		13
Oligophrenia agnogenetica group . .	2	8	22	19	51
Mongolism	8	2			10
Others	1		3	13	17
Totals	21 (15)	12 (9)	32 (25)	34 (28)	99 (73)

had been included. In my data, there is no correlation between the 4 categories of table 4 and the extent to which the individuals were officially registered. Thus, I do not think that if comparisons are made with *Sjögren*'s data all the 34 imbeciles (IQ 55–70) should be omitted.

Custodial care.

Of the 99 cross-sectional *propositi*, 32 were in institutions on September 1, 1949, including 2 males and 1 female institutionalized on account of their additional schizophrenic psychosis. A further 15 had been under custodial care earlier, including 1 male and 1 female who had additional schizophrenia. About 50 per cent of the oligophrenics had only been cared for in their homes. A survey of these data is shown in table 5.

Social capacity.

The extent to which the oligophrenics had been able to accommodate themselves socially was judged on the basis of their ability to carry out useful work. This, of course, is just one aspect of social accommodation, but perhaps the most important one. The data have been summarized in table 6. Omitting children below 12 years of age, about 21 per cent were able to support themselves with some social aid or supervision and a further 33 per cent were able to carry out some useful work. Three individuals only, all adult males and imbeciles, had criminal records (minor thefts) but had been exempted from punishment on account of their mental defect.

Biochemical tests.

It was possible to obtain urine samples for a test of phenylpyruvic acid of 23 random oligophrenics (cf. table 7). All these tests were negative. Though it cannot be excluded that phenylketonuria occurred in the investigation area, this possibility seems unlikely.

Marriage rates and reproduction.

According to the Swedish law, oligophrenic individuals are not allowed to marry. Naturally, such a prohibition can be effective only insofar as such individuals have been reported to the vicars' offices by some medical authority or are personally known to the vicars. In the latter case, only marriages of pronounced defectives are prohibited as, in regard to borderline cases, one cannot very well expect the vicar to decide who is mentally defective according

Table 5. Oligophrenia. All cross-sectional *propositi* (99). Institutionalization by explorative groups.

Category	Institutionalized per September 1, 1949		Previously institutionalized		Home care only		Total
	M	F	M	F	M	F	
Prob. environmental origin	2		1	1	2	2	8
Genetic spastic oligophrenia	4	1	4		1	3	13
Oligophrenia agnogenetica group	9	9	3		18	12	51
Mongolism	1	2			3	4	10
Others	2	2	4	2	4	3	17
Totals	18	14	12	3	28	24	99

Table 6. Oligophrenia. All cross-sectional *propositi* (99). Status in regard to working capacity per September 1, 1949.

Category	Able to support themselves		Unable to support themselves				Children below 12 years at home
	Without financial aid but with supervision	With financial aid and supervision	Assist with simple work	Cared for at home	Cared for in institution	In a school for the feeble-minded	
Prob. environmental origin			5		2		1
Genetic spastic oligophrenia			1	3	1	4	4
Oligophrenia agnogen. group	4	5	16	1	10	9	6
Mongolism						3	7
Others	3	5	4	1		3	1
Totals (99)	7	10	26	5	13	19	19

Table 7. Oligophrenia. All cross-sectional *propositi* (99). Examination of phenylpyruvic acide in the urine.

Category	Tested and negative	Not tested	Total
Prob. environmental origin	2	6	8
Genetic spastic oligophrenia	3	10	13
Oligophrenia agnogenetica group	15	36	51
Mongolism	1	9	10
Others	2	15	17
Totals	23	76	99

to the law. An investigation like the present one will therefore always disclose some individuals who have married. In this material, 3 males and 4 females were married (cf. table 8). Apart from the effect of the legal prohibition, the table shows that the marriage rate of the oligophrenics was rather insignificant. Of those 7 individuals who had married, 2 females had not been reported until after their marriage and then in connection with admission to a mental hospital on account of schizophrenic psychoses. One female (imbecile) had not been reported, and another had, after voluntary sterilization, obtained special permission to marry. Of the married males, one had not been reported until hospital admission due to schizophrenia, and two had been reported after their marriages on account of psychiatric examinations following criminal acts.

The analysis of the reproductive capacity of all adult oligophrenics of this population has been summarized in table 9. Altogether, the reproduction rate was considerably lower as compared

Table 8. Oligophrenia. Marriage rates. For each male 18 years of age or above and each female 16 years or above a control individual who was born in the same year and was living and resident of the investigation area on September 1, 1949, was selected from the parish register at random. The oligophrenic cases are also those living and resident on the same day, *exclusive* of those belonging to the groups "genetic spastic oligophrenia", "mongolism" and "of probable environmental origin" (cf. table 1.). None of the latter were married or had any children.

		Married	Unmarried	Per cent married	χ^2	P
Males:	Oligophrenic . .	3	31	8.8	26.78	< 0.001
	Controls	25	9	73.5		
Females:	Oligophrenic . .	4	16	20.0	12.1	< 0.001
	Controls	16	4	80.0		

Table 9. Oligophrenia. The same cases as in table 8. Number of children per individual as compared with their controls (here one male and one female control for each oligophrenic).

		No. of individuals	No. of children	Mean
Oligophrenic:	Extramatrimonial . .	54	8	0.15
	Intramatrimonial . .	7	32	4.60
Controls:	Extramatrimonial . .	108	16	0.15
	Intramatrimonial . .	85	384	4.50

Totals: 54 oligophrenics had 0.74 and 108 controls 3.70 children per individual.

with non-neuropsychiatric subjects. The number of children born per individual out of wedlock was the same for both groups (0.15). Those oligophrenics who had married, however, averaged the same number of children as the control individuals. The reproduction capacity may be expressed thus: 54 oligophrenics had issued 0.74 children per individual, whereas 108 comparable controls had 3.70. Consequently, the reproductive fitness can be estimated at 20 per cent.

The above results are in fair agreement with those reported by *Dahlberg* [1951] for oligophrenic individuals from the counties of Örebro, Kristianstad, Västerbotten and Värmland in Sweden. *Dahlberg* analysed the fertility of 1,650 individuals. Only a few of them, 1.5 per cent of the men and 9.3 per cent of the women, had children and but 1.4 per cent were married. The average number of children, per individual, aged 19 or above, was 0.11. On the other hand, the married women had an average of 5.1 children.

Thus it might be concluded that, insofar as adults are concerned, the selection against the trait oligophrenia, under prevalent circumstances, was rather pronounced. The total negative selection must, of course, have a higher value, as many oligophrenics die before reaching an age when they can have children.

Mortality.

For 51 oligophrenics who had died as residents of the investigation area prior to September 1, 1949 (i.e., during 1902–49), the average age at death was 30.8 years (23.7 years for 22 males and 36.1 years for 29 females). No less than 18 individuals had died before 15 years of age. With the exclusion of individuals who were diagnosed as genetic spastic oligophrenia and mongolism (conditions with especially heavy mortality), the average age at death was 28.5 years for males and 42.5 years for females with a total average of 37.0 years (observations: 15 males and 23 females). It can be concluded that the average length of life of the oligophrenics of this population was very much reduced. The observations concern only recognized and officially reported individuals, i.e., they had generally not been ascertained until they had reached school age. An unknown number of oligophrenics must have died unrecognized prior to that age. The life expectancy of unspecified oligophrenics thus cannot be calculated with sufficient accuracy, at any rate with the data available here.

The incidence of oligophrenia in the population.

The incidence of all types of oligophrenia as calculated on the total population per September 1, 1949, was:

i. Males 58/4,791 = 1.21 ± 0.16 per cent
ii. Females 41/4,190 = 0.98 ± 0.15 per cent.
For both sexes we obtain the figure of 1.10 ± 0.11 per cent.

At the calculation of the *morbid risk*, I have followed the same principles as *Sjögren* [1948], i.e., I have included only those oligophrenics who had reached the age of 10 years. Thus, in relation to the total population above 10 years of age, we have 72/6,340 or 1.14±0.13 per cent oligophrenics (exclusive of those with additional psychoses). This figure might be regarded as an estimate of the general morbid risk. If the 9 individuals with a main diagnosis of schizophrenia or involutional psychosis are also included, a morbid risk of 1.28 ± 0.14 per cent will be obtained. It should be observed that these figures do not include corrections for excess mortality.

In comparison with other studies, the general morbid risk of oligophrenia in the present population does not appear remarkable. As mentioned previously, existing differences of various reports are probably more due to differences of completeness of ascertainment and of diagnostic criteria. The figures of earlier reports average about 0.5 per cent (for a comprehensive survey see *Fremming* [1947]). The criteria which *Fremming* [1947] used in his own study were probably more similar to those of this study than to those of any other. However, *Fremming* estimated his upper limit at an IQ of 70–75, although his diagnoses appear to have been based on the same clinical and sociological evaluation as was used in this study.

Fremming [1947] estimated the morbid risk of oligophrenia for the average Danish population at 1.33 ± 0.18 per cent (1.46 ± 0.26 for males and 1.19 ± 0.24 for females). The same age limits as in this study were used in the calculations. For two North Swedish parishes (isolates), *Sjögren* [1935] calculated a risk of 1.4 per cent. In his West Swedish study, *Sjögren* [1948] found a risk of 0.80 ± 0.10 per cent and with an estimated correction for excess mortality, about 1 per cent. With reservations for the difficulties involved in the comparisons it seems probable that the incidence of oligophrenia in the investigation area does *not* deviate appreciably from that of most other populations (so-called general populations).

OLIGOPHRENIA OF PROBABLE ENVIRONMENTAL ORIGIN

None of the cases referred to this category was conclusive as measured by usual clinical standards. For the deceased oligophrenics, one history indicated mental defect due to birth trauma. Most histories of individuals belonging to this category were, however, very deficient insofar as birth, infancy and early childhood was concerned.

For the cross-sectional *propositi*, 7 histories indicated meningo-encephalitis and another one birth trauma as the cause of the mental defect. Although the information about these individuals was of much better quality, one must observe that the majority of the deliveries had occurred in private homes. The evaluation of the etiology, therefore, had to be based on information given by the parents (usually the mother) or in some cases also by the midwives. One is probably justified to conclude that a minimum of about 10 per cent of the oligophrenics of this population were defective on account of some sort of environmental injuries.

Case records.

168/49 K. O. L., male, born in 1932, died in 1948. Difficult delivery by forceps. Birth weight 2,500 g. Was a low grade, physically underdeveloped idiot. Could not walk or talk. Was probably blind. Had permanently involuntary movements of his arms. Had to be taken care of completely. Custodial care in a mental asylum from 1935 until 1948 when he died of marasmus.

16/49 J. A.V., male, born in 1905. Between 1 and 2 years of age he probably had meningo-encephalitis. His parents called it "child palsy". In connection with this disease, he had frequent convulsions. He remained a low grade idiot with destructive tendencies. Spent 5 years in a school for the deaf and dumb but was completely uneducable. Custodial care in a mental hospital since 1948. Examined by me in 1949: Low-grade, aggressive idiot. No contact could be established. Could not talk. Physical examination was impossible due to the patient's resistance.

46/49 A. G. Ä., male, born in 1931. Developed normally until 2 years of age. Mentally retarded after morbilli in 1933. Low grade idiot who had been in custodial care since 1937. My examination in 1946 did not reveal any gross physical or neurological abnormalities but, due to the patient's resistance, the examination was not quite satisfactory.

108/49 P. V. W., male, born in 1920. Between 6 and 12 months of age, he had a severe infectious disease with convulsions. After that, he was said to have been mentally retarded. In 1938 a psychometric test gave an IQ-value of 40–50. My examination in 1949 revealed definite signs of parkinsonism and some spasticity of his right leg. It seemed probable that his slow cerebration made him appear more mentally retarded than he actually was. His mental age was judged as corresponding

approximately to that of a child 10 years of age. He had a state pension on account of his mental defect but was able to work occasionally as a handy man.

113/49 S. O. K., male, born in 1920. Had convulsions when he was one year old. The history indicated meningo-encephalitis at the age of two. Had fever and convulsions. Before that he had walked but regressed after the disease and could not walk for two years. He was sent to a school for the feebleminded for two years but was unable to follow the instructions. My examination in 1949 revealed a severe myopia (–8 D. bilaterally) and a divergent strabismus of the left eye. His physical and neurological examination was otherwise negative. His intellectual development was judged as corresponding approximately to that of a child of 5–6 years of age. He was kind and well tempered and was able to assist with simple work in his home. Could attend to his own personal needs.

128/49 M. R. B., female, born in 1912. According to her mother, she developed normally until the age of 7. Could walk and talk at the age of two years. At seven, she had severe influenza during which she was unconscious for several days. After that she was different. Could not follow the instructions at school. She stayed at home and assisted in simple housework. Since 1938 she had received a state pension on account of imbecility. My examination in 1949 did not reveal any physical or neurologic abnormalities. Her mental development was judged as corresponding approximately to that of a child 7 years of age. She was kind and cooperative.

131/49 K. E. P., male, born in 1898. The history suggested meningo-encephalitis at the age of 4 years. Was said to have been mentally retarded since them. He also had become almost deaf after this disease. My examination in 1949 did not reveal any physical or neurologic abnormalities except that he was very hard of hearing. His mental development was judged as corresponding to that of a child of 6 years (at the most). He was able to carry out simple work under supervision.

235/49 U. M. J., female, born in 1945. At the age of 2 months this child, according to her mother, had a severe pertussis with protracted choking attacks. The parents did not think she would survive. She had appeared mentally retarded since then. She walked at the age of two years. Had always been difficult to handle. At the age of 4 she could say only a few words, as "mammy", "daddy" and "look". My examination in 1949 revealed a strabismus, a right-sided chronic otitis and some mongoloid features (although nothing to support a diagnosis of mongolism). Otherwise her physical examination was negative. She did not talk and took no interest in different objects. Although at this age the diagnosis must be guarded, it seemed probable that this patient was oligophrenic.

272/49, A. L. F., female, born in 1929. Difficult breech presentation. She had furthermore a severe infectious disease at the age of one year. After that, she became paretic in her left arm and leg. In 1933 she was examined at an orthopedic clinic and diagnosed as "hemiplegia spastica inferior sin". She spent 6 years in a school for the feebleminded where she was able to follow simple instructions. Her IQ in 1941 was 63. At my examination in 1949, there had been no change in her condition. She was able to carry out some simple housework under supervision.

All these cases except no. 235/49 had been noted in the parish registers.

OLIGOPHRENIA AGNOGENETICA GROUP

The composition of this group of 49 *propositi* who all were living and residents of the investigation area on September 1, 1949, was defined above (cf. also table 1, p. 350). Although the group might be considered as relatively homogeneous from a symptomatologic viewpoint, its biological homogeneity could not be further analysed by available clinical methods of investigation. It remained to examine whether a genetic analysis could supply further information.

To that effect, the parents and siblings of these *propositi* have been investigated. Table 10 shows the actual number of individuals who were ascertained and the extent to which they have been personally examined.

Table 10. Oligophrenia agnogenetica group (cf. table 1., p. 350). 49 *propositi* in 43 sibships. Survey of the total material. There are no double counts in this table. Personally examined individuals in brackets. The remainder have been investigated according to the principles given in part I of this report (*Böök* [1953c]). The total number of investigated individuals is 382. Age refers to September 1, 1949, or at disappearance from observation.

Age group	Propositi	Parents				Siblings				Grand Totals
		Dead	Moved	Living	Total	Dead	Moved	Living	Total	
0– 4						34		13	47	47
5– 9	4					8		20	28	32
10–14	11					6	2	25	33	44
15–19	6					6	23	13	42	48
20–24	3					2	16	12	30	33
25–29	6	2			2	3	4	9	16	24
30–34	2	1			1	4	3	10	17	20
35–39	5	4		4	8	1	1	6	8	21
40–44	3	2		7	9			8	8	20
45–49	1	2		6	8			4	4	13
50–54	4	2		10	12	2		6	8	24
55–59	2	4		6	10			1	1	13
60–64	1	6		6	12	2		1	3	16
65–69	1	7		3	10	1		2	3	14
70–74		3		1	4	1			1	5
75–79		5		1	6			1	1	7
80–84		1			1					1
Totals	49	39		44	83[1]	70	49	131	250	382
	(34)	(1)		(28)	(29)			(72)	(72)	

[1] Two fathers unknown, one mother had one further oligophrenic *propositus* out of wedlock.

Incidence of undifferentiated oligophrenia.

The *crude incidence* of "oligophrenia agnogenetica" was 0.63 ± 0.11 per cent for males and 0.50 ± 0.11 per cent for females. For both sexes we obtain a figure of 0.57 ± 0.08 per cent. If we include all undifferentiated cases, i.e. also those with additional diagnoses of psychoses or with suspected schizophrenic features, the corresponding incidences will be 0.84 ± 0.13, 0.64 ± 0.12 and 0.75 ± 0.09 per cent.

The *morbid risks* were calculated by exclusion of individuals below 10 years of age. For "oligophrenia agnogenetica" we obtain for males 0.81 ± 0.15 per cent, for females 0.59 ± 0.14 per cent and for both sexes 0.71 ± 0.11 per cent. For all undifferentiated cases the corresponding figures will be 1.10 ± 0.18, 0.81 ± 0.17 and 0.96 ± 0.12 per cent.

These figures do not include corrections for excess mortality.

Parents.

There are 43 parent-sibling combinations of which 83 parents were known. Among the parents the following neuropsychiatric conditions have been ascertained:

Conditions	Mothers	Fathers	Total
Oligophrenia	3[1]		3
Convulsive disease		1	1
Schizophrenia	2[1]	1	3
Involutional psychosis	1		1
Senile psychosis		1	1
Unknown psychosis	1	1	2

[1] One individual oligophrenia + schizophrenia.

As there are 4 sibships with two or more *propositi*, the number of experiences in regard to the parents was increased to 97. The calculation of the morbid expectancy for the different conditions gave these figures:

Oligophrenia	4.1±2.0 per cent
Convulsive disease	1.0±1.0 per cent
Schizophrenia	7.2±2.6 per cent
Involutional psychosis	1.0±1.0 per cent
Senile psychosis	1.0±1.0 per cent
Unknown psychosis	2.1±1.5 per cent

The expectancy of oligophrenia is somewhat higher but not significantly different from that of the general population (0.96 ± 0.12

per cent). *Sjögren* [1948] calculated a figure of 5.8 per cent for the parents of unclassified oligophrenics. Although the expectancy for schizophrenia appears somewhat high it does not deviate significantly from the population average (3 per cent). The figure of 7.2 per cent, furthermore, is somewhat misleading, as one schizophrenic mother had to be taken into account 4 times because she had no less than 4 living oligophrenic children.

The total expectancy for all kinds of psychoses was 11.3 $\pm$ 3.2 per cent. This figure is higher than that found by *Sjögren* [1948], which was 3.6 per cent, and might indicate an increase above the population average.

Siblings.

The morbid risk of undifferentiated oligophrenia for the siblings was calculated according to *Weinberg*'s method (table 11). The

Table 11. Oligophrenia agnogenetica group. *49 propositi* (cf. table 1, p. 350). Morbid risk of siblings irrespective of parental combination (although 3 mothers, only, were oligophrenic) calculated according to *Weinberg*'s method and with exclusion of all individuals below 5 years of age. 43 families.

Age group	Oligophrenia agnogenetica	Other neuropsychiatric cases	Normal siblings			Total
			Dead	Outmigrated	Living and resident	
0–4			(37)		(15)	(52)
5–9	2	1	6		21	30
10–14	3		5	2	28	38
15–19	5		6	25	16	52
20–24	4	2	1	16	10	33
25–29	3		3	4	10	20
30–34	3	2	5	2	9	21
35–39	2	1	2	1	6	12
40–44					10	10
45–49	1	1			3	5
50–54		2	1		4	7
55–59					1	1
60–64		2			1	3
65–w		1	2		2	5
Totals	23[1]	12[2]	31	50	121	237
Morbid risk for siblings 9.7$\pm$1.9 per cent[3].						

[1] Thereof 4 deceased and one case with the additional diagnosis of schizophrenia who also appears in the second column (= secondary cases of this analysis).

[2] Thereof 9 cases of schizophrenia or schizophrenia?, one genetic spastic oligophrenia, one involutional psychosis and one alcoholic psychosis.

[3] Standard error with correction for double counts.

calculated figure of 9.7 ± 1.9 per cent is significantly higher than the general risk (0.96 ± 0.12 per cent).

Sjögren [1948] calculated a morbid risk of 7.2 per cent for the siblings of unspecified oligophrenics of a West Swedish population. Emphasizing the difficulties of comparing different data of mental deficiency, he concluded that his figure by and large was in good agreement with those found by previous investigators concerning the expectation of more severe degrees of mental defect. The figure of 9.7 per cent of this study thus can be referred to the same category.

Of the 23 cases of oligophrenia appearing in table 11, only 5 were secondary cases according to the definitions for the genetic calculations. Two were low-grade idiots who were recorded in the parish register. One was probably an imbecile, according to information obtained from the Children's Aid Organization. Two further individuals were imbeciles and contracted schizophrenic psychoses at the ages of 26 and 27, respectively. However, as one of them did not show any signs of schizophrenia until after her emigration, she was counted only as oligophrenic.

An omission of those families in which one parent was oligophrenic did not affect the expectancy figure appreciably. It was reduced to 8.5 ± 1.9 per cent.

Among the siblings, there was a total of 9 individuals with schizophrenic or questionably schizophrenic psychoses. Calculated according to the method of *Dahlberg-Stenberg-Schulz* (cf. *Böök* [1953 c]), the morbid risk was 12.3 ± 3.8 per cent and, according to *Weinberg*'s abridged method (risk period 15–45 years), 10.4 ± 3.3 per cent. These figures are higher than the general risk of this population (3 per cent).

Sjögren [1948] calculated a morbid risk of schizophrenia of 2.8 per cent for his data. If one takes these risks at their face values and observes that the general risk in *Sjögren*'s population was 1 per cent, it is interesting to note that in both data the morbid risk of schizophrenia among the siblings of oligophrenic *propositi* was increased about 3 times. This might not necessarily mean some biologic connection between schizophrenia and mental deficiency but could be due to non-random matings and indicate that severe neuropsychiatric cases belong to a relative social isolate within the population.

An analysis of the distribution of the 49 *propositi* on different birth ranks did not show any significant deviations from what could be expected on the basis of random variation.

Comments on the "oligophrenia agnogenetica" group.

The clinical and genetic analysis of this group did not provide much useful information insofar as questions in regard to homo- or heterogeneity must be left unanswered. In a general sense one might conclude, as a number of other investigators have done on the basis of similar data, that the increased morbid risk for siblings of oligophrenic *propositi* indicates the cooperation of genetic factors which appreciably influence the variability in character between oligophrenic and non-oligophrenic individuals. The "undifferentiated oligophrenia of unknown etiology" of this population does not appear to be different from that of other populations. As one has reason to suspect that we are concerned with a biologically heterogeneous group, the data do not invite much genetic speculation.

In summary it might be concluded that the morbid risk of oligophrenia for siblings of individuals belonging to the category "oligophrenia agnogenetica" as defined was found to be 9.7 $\pm$ 1.9 per cent (irrespective of parental combination) and thereby significantly higher than the general risk of oligophrenia in the investigated population. This risk figure is strictly empiric.

MONGOLISM

For the total period of 1902–1949, 13 cases of mongolism were registered. Of these, 10 were living and resident on the cross-section date, two were dead and one had moved. The diagnosis was based on the presence of four or more of the following signs: (1) imbecility or idiocy, (2) a brachycephalic skull, (3) epicanthic fold over either eye, (4) fissured tongue, (5) presence of blepharitis, (6) transverse fold on either palm. All cases were examined professionally, 9 by me and 4 by other physicians. Some pertinent data concerning the mongoloid children of this study are given in table 12.

Crude incidence. In relation to the total population of the investigation area on the cross-section date, the frequency of mongolism was 10/8,981 or 1.1 per 1,000. This figure is higher than in previous surveys (cf. *Doxiades* and *Portius* [1938]: 0.14 per 1,000 in northern Germany and *Hanhart* [*op. cit. Schneider* [1949]]: 0.33 per 1,000 in Switzerland). The completeness of ascertainment, however, has varied considerably in the different investigations. The somewhat higher incidence in this population could, at least partly, be due to

Table 12. Mongolism. Survey of the total number of individuals registered for the period of 1902–1949 in the investigation area.

Family no.	Age	Sex	First registration through	Birth rank	Maternal age	Remarks
6/49	15	○	Parish register	5/5	39	living
13/49	7	□	Field study	3/3	48	living
76/49	8	□	Parish register	4/4	42	living
83/49	6	○	Field study	9/9	44	living
84/49	4	○	Field study	5/6	41	living
89/49	1	○	Field study	5/5	47	living
98/49	7	□	Field study	13/13	47	living
106/49	5	○	Parish register	10/10	47	living
147/49	11	○	Parish register	12/14	41	dead
197/49[1]	11	□	Parish register	1/1	43	dead
215/49	10	□	Parish register	7/7	39	living
222/49	6	○	Field study	3/3	42	living
279/49	1	□	Mental asylum	1/1	23	moved
Total		13	Total siblings	68	Mean 41.8	
			Total children	81		

[1] Father: involutional psychosis. For the rest of the cases no neuropsychiatric subjects occurred among parents or sibs.

the fact that no less than 40 per cent of all individuals were below 15 years of age. It should be recalled that the average life span of the mongoloid is only about 10 years. The incidence of mongolism per age group therefore decreases rapidly at increasing age.

Morbid risk. From a scientific viewpoint, it is more important to estimate the true incidence of mongolism among new-borns (= the general morbid risk). Although such an undertaking sounds simple, it has met with considerable difficulties, first because mongolism might be difficult to diagnose in the new-born and, secondly, because the doctors at the maternity clinics (from which most previous data were collected) hesitate to label a child as mongoloid unless there is no reasonable doubt about the diagnosis. Furthermore, such data are not always representative in respect to the age distribution of the mothers, as in many areas a greater part of the older mothers are delivered in their private homes. Consequently, the figures which have been calculated so far rather tend to be on the minimum side. According to *Penrose* [1949], European estimates have been of the order of 1 per 700. *Benda* [1949] reckons with a figure as high as about 1 in 300. *Carter* and *McCarthy* [1951] found an incidence of 1 in 667 among hospital births in England and Wales. *Øster* [1951]

reported 1 in 1,300 from the divisions of obstetrics at Copenhagen University Clinics, Denmark[1]. The latter figure is slightly biased, as the age distribution of the mothers was not representative insofar as the average age was lower than in the general population. As is well known, the risk of having a mongoloid child increases considerably with the increasing age of the mother. *Böök* [1951] found 1 in about 2,000 in a representative sample of hospital births in South Sweden, but this figure was considered to be much too low. However, it is fairly evident that mongolism is no rare occurrence.

In the present study, the registration of those mongoloid children who had died prior to our field work must be insufficient. The registration of the cross-sectional *propositi* should, however, be fairly complete, although I had no possibility to examine personally all children within the area but only those who were brought to the Child Welfare Clinics during the summer of 1949. For the rest, I had to rely upon the registration procedures which were described in part I of this report (*Böök* [1953 c]) and, in this connection, especially upon the information supplied by the midwives and the district nurses. It is noteworthy that of the 10 living cases who were disclosed, no less than 6 were unknown to official authorities. A first estimate of the morbid risk can be obtained by relating these 10 cases to the population below 10 years of age, letting the two mongoloids above this age to some extent substitute for those who might have been missed among the infants. This will give a figure of 1 in 264 or 3.8 per 1,000.

Another way of estimating the morbid risk is to determine the prevalence rate among all births to which the observed mongoloid children can be referred. All 13 were born during 1929–1948, and for this period a total number of 5,231 births were registered in the area. The morbid risk thus would be 1 in 402 or 2.5 per 1,000. This figure represents a minimum.

The true risk can be assumed to lie within the limits of these estimates. It thus appears somewhat higher than most previous estimates. One reason should be pointed out why one should expect a somewhat higher incidence in this population. For comparable periods (1931–1948), the incidence of women aged 40 and above giving birth to children was 9 per cent for the rural parts of Norrbotten county against 7.5 per cent for all rural districts in Sweden.

[1] In his monograph just published (*Øster, J.*, Mongolism. Danish Science Press, Ltd., Copenhagen 1953, 206 pp.) the incidence of mongols among the newborn in Denmark was calculated at 1 : 618 or 1.6 per 1000.

The empiric risk of mongolism at a maternal age above 40 is substantial.

If we neglect multiple births as being of no consequence here, we can estimate that of the above-mentioned 5,231 births, 9 per cent or 471 were of women aged 40 or above. Of these 471 children, at least 10 were mongoloid (cf. table 12), implying a morbid risk of 2.1 per cent. The 3 remaining mongoloids thus should be related to 4,760 birth of women below 40 years of age, implying a risk of but 0.06 per cent. These risk figures, related to maternal age, agree very well with my previous estimates for the white population in the USA (*Böök* and *Reed* [1950]) at a sample frequency of 1 in 500 in the general population. One seems justified in anticipating that a general morbid risk of 1 in 500 new-born should rather be a conservative estimate.

The empiric risk figures have been summarized in table 13. As there has been no reason to suspect that the mongolian idiot occurring in this region was in any way different from mongoloids from other populations, the figures can be considered as generally valid.

Table 13. Empiric risk of mongolism in relation to mother's age.

Mother's age	Risk of having a mongoloid child
< 40	0.06 per cent
> 40	2.12 per cent
All ages	0.25–0.50 per cent

Familial and other data. The number of observed individuals is, of course, too small for an analysis pertinent to the etiology of mongolism. A study of table 12 will convince the reader that the well known maternal age factor and the shift to the right in the birth ranks are amply demonstrated without the use of more elaborate statistics. No further cases of mongolism were found among the 68 siblings. All parents, except one father (involutional psychosis), were healthy and normal people. Consanguinity between the parents of the *propositi* was not found in any family, neither could we find any closer consanguinity between the different families. All cases of mongolism seemed to have occurred in a sporadic fashion in this population.

One of the hypotheses that have been offered to explain the etiology of mongolism is not contradicted by any known facts and therefore deserves serious attention. I believe *Kemp* [1944] was the

first to suggest that mongolism could be due to a dominant mutation (of course, not necessarily a *gene* mutation). In spite of a considerable amount of work and energy devoted to the task of proving that some endocrine disturbance or pathologic change of the female genital apparatus would be the cause (*Benda* [1949] and others), the facts do not sufficiently support the theories. (cf. my review of Dr. *Bendas* monograph in Amer. J. Human Genetics (2:91–93:1950). It would be extremely difficult to produce definite proof of the mutational origin of mongolism, as these individuals very seldom reproduce. However, of 4 mongoloid females who are known to have had children (cf. *Lelong* and co-workers [1949] and *Sawyer* [1949]), one had a mongoloid child. The fact that the other three had normal children is by itself interesting and does not favour the endocrinopathic theories. The mutation hypothesis tallies also with the 100 per cent concordance of monozygotic twins and the nearly 100 per cent discordance in dizygotic.

Assuming that this hypothesis is correct, the mutation frequency could be calculated from the equation:

$$u = 0.5\,(1-f)x$$

where f is the reproductive fitness (in this case practically 0) and x the frequency of the trait (the equation is valid only if the incidence of affected homozygotes can be neglected). Taking the observed incidence in the present population, the mutation frequency would be $1.3–1.9 \times 10^{-3}$ gene per generation. This would be a very high mutation rate but not necessarily a unique situation (cf. the discussion by *Böök* [1953 a]). However, the figure is somewhat misleading since the age-specific morbid risk must be taken into consideration. This would mean that gametes of young individuals (say below 40) would display a mutation rate of approximately 3×10^{-4}, while gametes of individuals above 40 would mutate with a rate of about 10^{-2}, or a hundred times more often. Although these consequences may at first appear fantastic, there is nothing to indicate that the maternal factor in mongolism might not be some mechanism that increases the spontaneous mutation rate.

In summary, the data on mongolism from this population indicate a crude incidence of 1.1 per 1,000 and a general morbid risk of between 2.8 and 3.8 per 1,000 new-borns. Age-specific morbid risks were estimated at 0.06 per cent for mothers below 40 years of age and at 2.1 per cent for mothers 40 years of age or above.

GENETIC SPASTIC OLIGOPHRENIA

During the present study, it was disclosed that some 10 per cent of the oligophrenics displayed signs of infantile spastic cerebral palsy. It was then decided to subject this rather well-defined group to a special clinical and genetic analysis.

Since *Little* in 1843 and 1862 (*op. cit. Penrose* [1949]) described infantile spastic cerebral palsy which he believed to be due to injury at birth, a large number of studies have been made on this topic. From a neurologic point of view, this syndrome implies the occurrence of spastic motor defects, with or without athetosis or choreiform movements during infancy or early childhood. This symptom-complex is due to brain pathology caused by a number of different factors. The etiologic mechanisms, in the focus of interest at present, have been summarized by *McGovern* and *Yannet* [1947] thus: (1) developmental anomalies, which may be genetically determined in a small number of cases; (2) cerebral trauma during the birth process; (3) cerebral degenerations, and (4) acquired postnatal cerebral abnormalities, mainly traumatic or infectious.

From a clinical viewpoint, the cerebral spastics have been separated into two groups, namely (1) symmetric conditions, including diplegia and paraplegia and (2) asymmetric conditions, including hemiplegia, mono-, tri- and quadriplegia.

Previous investigations (*cerebral palsy in general*).

A comprehensive review of the literature up to 1938 was given by *Thums* [1939]. Already in 1888–93, *Freud* (cf. *op. l.c.*) in a number of papers emphasized the heterogeneous character of infantile cerebral palsy and differentiated between hemi- and diplegic forms, although without ascribing to either type any particular type of etiology. The terms diplegia and paraplegia have often been used without clear definitions. At closer examination, some spasticity or hyper-reflexia of the upper extremities is often revealed in so-called paraplegic individuals. The subdivision into symmetric and asymmetric conditions, as mentioned above, appears more important.

Asplund [1939] reported 104 cases admitted to an institution for disabled children in Stockholm, Sweden, during 1921–37. Forty-five of these were paraplegics (43 per cent). Of all cases, 91, or 88 per cent, were congenital. The mental endowment was judged as good in 17 per cent, as fairly good in 28 per cent, and as lowered in 55 per cent.

The etiology of cerebral palsy was studied by *Evans* [1948]. His

data comprise 114 cases of whom 40 per cent were spastic para- or tetraplegics. The etiology was known or probable in 17 cases. These were (1) postnatal hydrocephalus (4 cases), (2) meningitis (1 case), (3) encephalitis (2 cases), (4) hemolytic disease of the new-born (8 cases) and (5) hemorrhagic disease (2 cases). As far as the symmetric spastic cases were concerned, no significant causes were disclosed. The group comprised 38 cases of para- and tetraplegia. These were compared with 50 normal children in regard to parental age, abortions of the mother, birth rank, prematurity, labor and neonatal conditions. The only probable difference was that there were more prematures among the spastics than among the control children. However, on the basis of such findings there is hardly any justification to regard prematurity as a cause. Children with all kinds of fetal pathology are more often born prematurely than normals (cf. *Böök* [1951]). Thus, prematurity could be an effect of the fetal pathology rather than its cause.

McIntyre [1946] examined 290 males and 210 females with cerebral palsy. From a neurologic point of view they were distributed as follows: 56.6 per cent quadriplegia, 6.0 per cent triplegia, 25.6 per cent hemiplegia, 9.0 per cent diplegia, 1.6 per cent monoplegia and 1.2 per cent other types. The average age of these individuals was 9.8 years. According to special psychologic tests by *McIntyre*, 27.6 per cent were definitely feebleminded (mentally deficient) and a further 5.8 per cent borderline cases.

Levin and co-workers [1949] reported a population survey from Schenectady County, N.Y., USA. Through medical and welfare agencies and practising physicians, a total of 125 cases of cerebral palsy were ascertained. The crude incidence was 91 per 100,000, the population of the county being 137,000. For a more intense study, a random sample of families residing in the area was selected. A total of 22,528 individuals was studied. Of the previously known cases, 20 belonged to this sample and an additional 14 cases were disclosed and examined by a competent neurologist. The actual crude incidence thus would be 152 per 100,000. Complete data were available on 121 cases. Of these, 10, or 8 per cent were defective because of cerebral trauma or infectious disease suggesting meningo-encephalitis. In 111 cases the symptoms had appeared at birth or within the first 6 months. Excluding all postnatal cases and putting the remainder in relation to the total population divided by 5-year groups, the incidences were for the age group 0–4 years 251, and 5–9 years 591 per 100,000. *Levin* concluded that an incidence of 5.9 per 1,000 would come close to the

true rate at birth. The lower rate for the age group 0–4 years could be explained by difficulties of ascertainment insofar as infants and small children are concerned. An analysis of the economic and occupational status of the families revealed no important issues. Of all the cerebral palsied individuals, 22 per cent were or had been able to attend regular schools and maintain their proper grade, 17 per cent were or had attended regular schools but had fallen two or more years behind their grade, 34 per cent had to attend special classes or had been committed to special institutions due to severe mental or physical incapacity. Finally, 27 per cent had not been able to attend any school at all. A total of 45 per cent were diagnosed as mentally defective. Fourteen cases, or about 10 per cent of all, were paraplegics.

Genetic studies. A number of single sibships in which two or more cases of cerebral palsy have occurred have been reported in the literature. The inherent bias of such recordings deprive them of much genetic value. *Faber* and *Mueller* (cf. *Thums* [1939]) studied the siblings of 31 children with *Little*'s disease and found no further cases in these sibships. *Thums* [1939] made an adequate twin study and was able to examine 13 monozygotic and 18 dizygotic twin pairs of whom the *propositus* had infantile cerebral palsy. One twin pair of each category was concordant. Thus, the results of genetic studies have so far been essentially negative. However, it is necessary to remember that the groups which were studied have been very heterogeneous. *Thums*' data, for example, include paraplegics, hemiplegics, tetraplegics and even one case of microcephaly. The motor symptoms were in some cases combined with extrapyramidal signs and/or mental deficiency. For one of his *propositi* congenital syphilis was probably the only cause.

In summary: Investigations of the compound group of cerebral palsy thus have failed to reveal any common etiology. It is most likely that we are concerned with a rather variable syndrome which may be due to a large number of diverse factors, most of which are unknown. Some 30 to 50 per cent of the cerebral palsied appear to be appreciably mentally deficient. One study from the U.S.A. indicates an incidence at birth of about 6 per 1,000. No facts have been found to indicate that genetic factors cause cerebral palsy in the majority of cases.

Previous investigations of cerebral palsy with mental deficiency.

Whereas the studies of the group of infantile cerebral palsy at large have given no clear indications that genetic factors might be

involved in the etiology, the situation appears different if one studies mentally defective individuals with these motor defects.

In his study of 1,280 cases of mental defect, *Penrose* [1938] found 66 cases of diplegia of prenatal origin. Of these, 11 had mainly or wholly extrapyramidal lesions. In all 66, the condition was stationary during the period of observation. Only 4 out of the 132 parents were mentally defective and, in addition, the differences between the normal and the idiot and imbecile siblings were more clear-cut as compared with the sibships of undifferentiated oligophrenic *propositi*. In several families, both the *propositus* and a sibling displayed bilateral pyramidal disease. However, a diplegic sibling did not always appear mentally defective. In 6 families, the parents were consanguineous. In some families, only the diplegics were mentally defective. These findings suggest that recessive genetic types of mental deficiency with spastic diplegia occur.

In 1943 *Wolfslast* reported a pedigree with five males all afflicted with spastic diplegia. Also, extrapyramidal and cerebellar signs were noted in some cases. At least two cases were mentally defective. The type of transmission was interpreted as sex-linked recessive.

Yannet [1949] studied 157 consecutive cases of infantile cerebral palsy with severe mental deficiency, admitted to the Southbury Training School, Conn., USA. Their average IQ was 25. Birth trauma or postnatal nervous system infections were found to be of etiological significance in about one third of the cases with asymmetric spastic involvement. In regard to the symmetric hypertonic palsies, no indication of specific natal or postnatal etiologic factors was found.

Malzberg [1950] made a statistical study of 544 cases of cerebral palsy from schools for the feebleminded in the State of New York, USA. These cases comprised 2.9 per cent of the total number of individuals who had been committed. About 45 per cent of the cases were idiots, and about 38 per cent were imbeciles. *Malzberg* found a slight and probably insignificant relative excess of first-borns, whereas the birth ranks no. 5 and over were probably over-represented.

A significant genetic study was made by *Hanhart* [1936]. This report is of special interest in connection with this study, as it deals with a type of cerebral diplegia with mental deficiency discovered in a small Swiss isolate. Seven cases who all belonged to the same pedigree complex were studied by *Hanhart*. The clinical picture

appeared very homogeneous and was characterized by spastic motor defects of the legs, probably congenital, speech defects and mental deficiency. No indications of birth injuries or other exogeneous causes were disclosed. The seven cases belonged to four sibships which could be connected through a common ancestral pair who lived at the end of the seventeenth century. Consanguinity between the parents was established for all four sibships. The data fully support *Hanhart*'s conclusion that the condition must be due to a single recessive gene difference.

In summary the accumulated data on infantile cerebral palsy indicate the pronounced heterogeneity of this clinical concept. It should be appreciated that questions about etiology and symptomatology refer to a group of conditions which just happen to have some outstanding motor defects in common. These defects apparently may be due to a wide variety of different causes as, for instance, birth injuries, meningo-encephalitis, Rh-isoimmunisation and prenatal lesions. It appears that asymmetric conditions would more often be due to birth injuries, or neo- and postnatal brain damage. The etiology of the symmetric conditions is practically unknown. From a genetic viewpoint, the most promising approaches have been made when the *propositi* were selected from mentally deficient populations. A few studies support the hypothesis that specific clinical and genetic entities exist which are characterized by symmetric spastic motor defects combined with mental defect. There are, however, as yet no data which indicate that genetic factors operate among asymmetric and not mentally defective cases. Finally, it should be recalled that so called cerebral palsy disables more individuals than poliomyelitis. From a public health point of view, the problem is therefore of great significance.

Case reports.

For each individual examined by me a complete history of the mother's condition during pregnancy, delivery, diseases of infancy and childhood and subsequent diseases was secured. My examination included a clinical evaluation of the degree of mental retardation, a physical examination and a neurologic study. Positive findings only will, as a rule, be reported. However, it should be mentioned that in no case did the ophtalmoscopic study reveal any pathology. The superficial sensibility appeared normal in all cases.

Sibship no. 19/49.

O. A. K., male, born in 1913. His mother said he had "child palsy" as a baby. At the age of one year he had convulsions (probably spasmophilia). Mentally retarded from early infancy. Started to walk a little about the age of 5. Could not talk plainly at 14. In 1928 he was admitted to a school for the feebleminded. In 1930 his IQ was 53 *(Terman-Merill)*. He was a nice and well-tempered boy who learned to read and write a little. He displayed a moderate spasticity of both legs and some difficulty in walking. Discharged in 1930.

Examined by me in 1949. A kind and cooperative imbecile. Could read simple sentences but did not understand much of what he read. Could write his name, pointed out with some difficulty the even hours on a watch and knew the coins and bills. He was able to attend to his own personal needs and did some simple handy-work around the house. Had no complaints, except about difficulties in walking. Felt stiff in his legs and had to rest after walking some 20 yards. – His body type was leptosomic. Psychomotorically rather sluggish. He had 4+ ankle jerks and moderate patellar clonus bilaterally. Increased muscle tonus of both legs. His gait was unsteady and he walked with short steps, somewhat broadbased.

Sibship no. 30/49.

G. S. K., female, born in 1910, died in 1913. She took no interest and appeared idiotic from birth. She was paralysed in both legs and never learned to stand, walk, or sit. She never spoke a word. She died of some infectious disease, probably pneumonia, and was never seen by a doctor. Her mother said she displayed the same signs as her affected brothers.

G. I. K., male, born in 1912. Mentally retarded from birth. Admitted to a school for the feebleminded in 1923, where he has found to be uneducable. He could not attend to his own personal needs except for taking food. Was incontinent and could not talk. He had knock knees and flat feet. His gait was spastic-paretic and he had exaggerated knee jerks. He was diagnosed as having *Little*'s disease. In 1933 he was transferred to an asylum.

O. I. K., male, born in 1914, died in 1949. Mentally retarded from birth. Never learned to talk or walk. In 1928 admitted to a school for the feebleminded. Quite uneducable. Flat feet. Could walk a few steps with help. Exaggerated knee jerks. Spent most of his time in bed and made no trouble. In 1933 he was transferred to an asylum where he died in 1949.

I. S. K., male, born in 1924. Mentally retarded from birth. Could walk a little at 4–5 years of age but never talked. In 1935 he was admitted to a school for the feebleminded. Quite uneducable. Except for taking food he was not able to attend to his own personal needs. Had periods when he was stubborn, irritated, and tore his clothes. Displayed sometimes involuntary movements. Could say nothing intelligible but "mammy" and "daddy". His gait was spastic-atactic. Discharged home in 1947.

Examined by me in 1949. Low-grade idiot. Athletic body type. Knee and ankle jerks 3+ bilaterally. *Chaddock* was extensor on the right. Typical spastic gait. Increased muscle tonus of both legs. Examination of the cerebellar system was negative. He displayed no involuntary movements at the examination. His mother said he was mostly calm and easy to handle at home.

Sibship no. 45/49.

J. M. V. D., female, born in 1922. Mentally retarded from birth. Could not sit up before 6–7 years of age. Never learned to talk. Had diphtheria at the age of six. Displayed diverse involuntary movements of her arms, legs and tongue. She was unable to attend to her own personal needs. She was admitted to a school for the feebleminded in 1935. Quite uneducable. Transferred to an asylum. In 1949 she had some kind of fits, described as twitching of arms and legs, but she did not lose consciousness.

Examined by me in 1949. Low-grade idiot unable to talk intelligibly. Dysplastic body type with rather short legs. Knee and ankle jerks were 4+ with increased reflexogenic zones. Plantar reflexes (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*) were extensor bilaterally. Symmetrically increased muscle tonus of both legs and, although much less pronounced, of both arms. She could not walk and could barely stand with aid. Pronounced muscular weakness of arms and legs. Pronounced flat feet. Both feet were fixed in equinus position due to muscular contractures. She displayed some twitching of the facial muscles.

Sibship no. 63/49.

H. A. L., female, born in 1937. Mentally retarded from birth. Never learned to talk or walk.

Examined by me in 1947. Low-grade idiot who had to be taken care of completely. Grimaced and made some unintelligible sounds, but could not talk. Now and then she displayed slight athetotic movements of arms and legs. She could stand and walk a few steps with aid. The legs were adducted, crossing in front of one another with the knees scraping together. The muscle tonus of the legs was increased. She had a rather pronounced muscular atrophy of both lower legs. Knee jerks were 4+ with increased reflexogenic zones, ankle jerks 3+. Moderate foot clonus. Plantar reflexes were extensor bilaterally (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*).

Sibship no. 107/49.

S. H. I. Y., male, born in 1933. Mentally retarded from birth. At the age of 9 months the mother noted he did not move his legs. She believed he had had "child palsy". He was late in attempting to walk and talk. He could not attend school and was admitted to a school for the feebleminded in 1946. His IQ was 48 (*Terman-Merill*). He had a pronounced kypho-scoliosis. Spasticity of both legs with 10° flexion contractures of both knees. He made good progress and was sent back home in 1948 to attend a help class at the public school. However, according to the teacher, he was hardly able to follow the program.

Examined by me in 1947 and 1949. Imbecile, friendly and cooperative. Thoracal kypho-scoliosis. Knee contractures as above. Moderate atrophy of both lower legs. Pedes plani-valgi. Knee and ankle jerks 4+ with patellar and ankle clonus on both sides. Plantar reflexes extensor on both sides (*Babinski*, *Oppenheim*, *Gordon*, *Chaddock*). Increased muscle tonus of both legs. Typical spastic gait with short steps and adducted legs. Could walk by himself with the aid of two orthopedic canes.

K. G. Y., male, born in 1936. Mentally retarded from birth. When he was two years old his mother observed that he was weak in his legs. She thought he had

"child palsy". Later he learned to walk a little but with considerable difficulties. He could not attend the public school. In 1945 and 1946 he was admitted to an orthopedic clinic. He had pronounced spasticity of both legs. Could walk with a cane. Due to fixation of his feet in equinus position, bilateral achillotomies were made. Later he got orthopedic shoes. In 1946 he was admitted to a school for the feebleminded. His IQ was 52 (*Terman-Merill*). He had a stable and pleasant temperament. He made good progress, and in 1948 he was discharged to attend a help class at the local public school. However, he experienced considerable difficulties in following the program there.

Examined by me in 1947 and 1949. Friendly and cooperative imbecile. Cryptorchidism. His left leg was somewhat shorter than his right. Moderate atrophy of the muscles of both lower legs. Left-sided pronounced pes plano-valgus. Knee and ankle jerks 4+. Sustained bilateral foot clonus. Plantar reflexes were extensor on both sides (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*). Typical spastic gait. Could with some difficulty walk by himself.

Sibship no. 144/49.

E. S. F., male, born in 1909, died in 1922. Mentally retarded from birth. Never took any interest. Had to be attended to in all respects. Neither talked nor walked. His legs were paralysed. Examined by the district physician in 1913: Could not walk or talk. Since birth he had been lying in bed almost in a fetal position. Cried like a new-born when disturbed. Undersized.

E. R. F., female, born in 1922, died in 1947. Mentally retarded from birth. At the age of 3 months she had convulsions during a short period. Tried to walk at the age of 4. Never talked. Had to be attended to in all respects. In 1945 she was admitted to an asylum for uneductable oligophrenics.

Examined by me in 1946. Low-grade idiot with unstable temperament. Sometimes aggressive and destructive. Had to be kept in bed permanently. During 1945 she had a total of 5 grand mal seizures. She was of leptosome-hypoplastic body type. Muscular contractures of both hips. She had pedes plani-valgi with both feet in equinus position. Her right pupil was somewhat larger that her left. Knee and ankle jerks were 4+. She had a sustained patellar and foot clonus on both sides. Of the plantar reflexes, *Babinski* was extensor on the right, no reaction on the left. She could stand and walk a few steps, displaying a typical spastic gait. X-ray examination disclosed bilateral pulmonary tuberculosis. She finally died of this disease.

Sibship no. 155/49.

J. L. U., male, born in 1925, died in 1934. Mentally retarded from birth. Admitted to a school for the feebleminded in 1933. He was of about the same size as a 3–4–year–old child. The legs were adducted, crossing in front of one another. Pronounced flat-feet on both sides. Did not grasp. Could neither walk nor sit. Spastic paralysis of both legs. Low grade idiot. In 1932 he was diagnosed as having *Little*'s disease by the district physician.

Sibship no. 159/49.

H. I. P., female, born in 1916, died in 1923. Mentally retarded from birth. Never took any interest. Had to be attended to in all respects. She never walked or

talked. Was bedridden all her life due to paralysis of both legs. She was never professionally examined.

Sibship no. 172/49.

M. U., male, born in 1920, died in 1923. Mentally retarded from birth. Never took any interest and appeared profoundly idiotic. Was paralysed in both legs. Was not professionally examined.

G. G. U., female, born in 1937, died in 1947. Was a low-grade idiot from birth. Had to be attended to in all respects and was constantly bedridden. Both legs were paralysed and she never made any attempts to walk or sit. She was lying with both legs adducted and bent one over the other. She never took any interest and was unable to recognize her parents.

Sibship no. 218/49.

The mother who died in 1949 at the age of 42 years carried the diagnosis of schizophrenia (catatonic form) + imbecility.

H. O. A., male, born in 1933. Mentally retarded from birth. In 1939 admitted to a school for the feebleminded. Was found to be uneductable and transferred to an asylum. His IQ in 1949 was 33 (*Terman-Merill*).

Examined by me in 1949. Stable temperament, friendly and cooperative. Pronounced imbecility. Could answer very simple questions only, and also do some simple errands. Could neither read, write nor count. Did not know about hours, minutes, coins or bills. Hypoplastic habitus. Moderate atrophy of both lower legs with increased muscle tonus. Knee and ankle jerks 4+ on both sides. Sustained patellar clonus bilaterally. Plantar reflexes: *Babinski* was extensor? on the left, flexor on the right, *Chaddock* extensor on the left. He displayed a typical spastic gait. With some difficulty he could walk without aid. He had moderate pedes plani-valgi.

G. R. A., male, born in 1938. Mentally retarded from birth. Had measles in 1941 with no sequelae. At the age of 15 months he was examined by the district physician. Could not stand or sit without help. Appeared like a 3-months-old baby. In 1939 he was treated in an orthopedic outpatient department on account of a right-sided congenital clubfoot. The same year he was admitted to a school for the feebleminded. Could not sit or balance his head. As he was completely uneducable, he was transferred to an asylum.

Examined by me in 1949. Low-grade idiot. Could not talk. Had to be attended to in all respects. Right-sided severe clubfoot with muscular contractures. Left-sided pronounced pes plano-valgus. Generally increased muscle tonus of all extremities. Reflexes: biceps, triceps and radialis 3+ on both sides. *Babinski* hand sign positive on both sides, knee and ankle jerks 4+ with sustained patellar and ankle clonus on both sides. Plantar reflexes were all extensor (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*). Moderate atrophy of the muscles of both lower legs. He could stand and walk a few steps with aid.

Sibship no. 219/49.

U. A., female, born in 1943. Mentally retarded from birth. Could say a few words at the age of 4–5 years. Had never been able to walk, crawled around helping herself with her arms. In 1949 she could say a few short sentences.

Examined by me in 1949. Appeared to be a low-grade idiot of stable and friendly mood. She grasped objects and played with some keys. Blew out a lighted match which was held in front of her. She had bilateral moderate clubfeet. The muscles of the lower legs were moderately atrophic and hypertonic. Knee jerks 3+ with increased reflexogenic zones on both sides, ankle jerks 2+. Plantar reflexes were all extensor (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*). She could stand up with aid but was unable to take a single step. A test for phenylpyruvic acid in the urine was negative.

K. M. A., male, born in 1947. Appeared mentally retarded from birth. Had made no attempts to stand or walk. Could sit without aid. Could say "mammy" and "daddy".

Examined by the writer in 1949. Was able to say a few words. Was afraid of a lighted match held in front of him. Grasped after objects. Could sit and balance his head but could not walk. Could raise himself if helped. Moderate clubfeet. Knee jerks were 4+ with increased reflexogenic zones. Increased muscle tonus of both legs. Phenylpyruvic acid test in urine was negative.

Sibship no. 225a/49.

A. G.-S., male, born in 1906. Was said to have had "child palsy" when he was 2 years old. Between 1909 and 1923 he was said to have had grand mal seizures. He was mentally retarded from birth and a deaf-mute. He began to walk at the age of 7. He spent 5 years in a school for the deaf and dumb but was unable to learn anything. He did not take interest in anything but food. He had an unstable temperament with episodes of *temper tantrums*. Subsequently he became rather difficult to handle, and in 1944 he was admitted to an asylum for uneducabl eoligophrenics. Deaf-mute. Spastic paresis of both legs. Patellar and foot clonus on both sides. Spastic paresis of both legs. Patellar and foot clonus on both sides. Spastic, unsteady gait. Slight tremor of both hands. Followed an object with his eyes. Knew how to hold a pen but could not write. His *Wassermann* reaction was negative. The hospital diagnosis was infantile spastic diplegia (*Little*).

Examined by me in 1949. Low-grade idiot. Knee and ankle jerks 4+, patellar and foot clonus on both sides. Increased muscle tonus of both legs. Plantar reflexes extensor on both sides (*Babinski*, *Oppenheim*, *Gordon* and *Chaddock*). Typical spastic gait. Probably completely deaf. Phenylpyruvic acid test in urine was negative.

Sibship no. 225b/49.

E. J. G.-S., half-sister of the above case, born in 1927, died in 1945. Protracted delivery but no special complications. Said to have had blood in the urine as a child. Measles in 1933, chicken-pox in 1934. She was mentally retarded from birth and never learned to talk. Attempted to walk at the age of 4. Admitted to a school for the feebleminded in 1934. As she was a low-grade idiot who had to be attended to in all respects, she was transferred to an asylum in 1939. She was able to walk with difficulty and displayed a spastic paralysis of both legs.

Sibship no. 242/49.

B. I. U., female, born in 1940. She was mentally retarded from birth. Never learned to talk, sit or walk. Had to be attended to in all respects.

Examined by me in 1949. Low-grade idiot who took absolutely no interest. Very thin and generally hypoplastic. Rather small head with a cranial circumference of 44 cm. She displayed athetotic movements of both arms. Bedridden with her legs crossed, flexion contractures of hips and knees. Knee and ankle jerks were 4+ with patellar and ankle clonus on both sides. Generally increased muscle tonus. She had a convergent strabism of her left eye. She was unable to stand or walk.

Sibship no. 266/49.

S. O. U., male, born in 1931, died in 1938. Mentally retarded from birth. Said to have had convulsions when 3 days old. Admitted to an orthopedic clinic in 1938. The diagnosis was infantile spastic diplegia + imbecility. Admitted to a school for the feebleminded in 1938. Could say a few sentences. Uneducable. He had spastic muscular contractures of both knees. Could raise himself and walk with help. Exaggerated knee jerks. Plantar reflexes questionably extensor. His temperament was usually stable, but sometimes he was rather stubborn. He died in a status epilepticus.

Sibship no. 274/49.

U. A. O., male, born in 1922, died in 1942. Mentally retarded from birth. Admitted to a school for the feebleminded in 1933. Low-grade idiot. Could not talk and had to be attended to in all respects. Bilateral cryptorchidism. Displayed a spastic paralysis of both legs, but could walk, although with difficulty. In 1938 he was transferred to an asylum.

Symptomatology of the observed cases.

Mentality. The majority were very low-grade idiots and only a few were imbeciles. Their temperament appeared usually stable, although *temper tantrums* were observed in a few cases. All cases were socially incapacitated, and the majority was in need of permanent custodial care. Two individuals out of the 24 observed had *grand mal* seizures, and a further two were suspected of having convulsive disorders. These four were all low-grade idiots.

Unless specificly stated otherwise, the following remarks refer to the 13 cases examined by me.

Foot deformities. Uni- or bilateral *pes plano-valgus* occurred in 6 cases, clubfoot in 5 cases.

Neurological studies. The examination of the cranial nerves did not reveal any significant pathologic signs. Ophtalmoscopic studies revealed no eye fundi pathology. The reflexes of the upper extremities were moderately hyperactive in three cases only. The knee jerks were 3+ in two cases and 4+ in nine. The ankle jerks were 2+ in four, 3+ in two and 4+ in seven cases. All these reflexes were symmetric. Symmetric patellar and/or ankle clonus was present in nine cases.

Extensor plantar responses were observed in ten cases. In all cases the muscles of the legs were hypertonic. Some increase of muscle tonus of the upper extremities was found in three cases.

Involuntary movements, indicative of extrapyramidal damage, were observed in four cases.

The superficial sensibility which as a rule could be tested for pain only was apparently normal in all cases. No pathological signs were observed on examinations of the cerebellar system. Naturally, it is granted that all examinations which require the close cooperation of the patient are difficult to perform with mentally defective individuals. These statements therefore concern only major deviations from normality.

A moderate muscular atrophy was observed in four of the 13 cases. There were, however, no signs of progressive wasting.

Apart from the mental retardation, the most important functional impairment concerned the gait. Information about this item was available for all 24 cases. Of these, 9 were completely unable to walk, 5 could walk a few steps if aided by another person, 2 could walk with a cane or some other mechanical aid, 7 walked without support but with appreciable difficulty, and, finally, one patient had only a moderately abnormal gait. The character of the gait ranged from a typical "scissors gait" with adducted legs, short steps and slow progression, to one with moderately expressed spastic features.

The condition appeared congenital and stationary in all cases. The first sign noted by the parents was sometimes the impairment of the legs. This sign was often not observed until the child was about to start walking. Most cases, however, were described as mentally retarded from birth or early infancy.

In summary the symptomatologic picture of this syndrome might be described thus: a congenital and stationary condition characterized by symmetric spastic motor defects predominantly of the legs combined with severe mental defect.

Etiology.

None of the histories of these individuals were suggestive of pathological pregnancy of the mother, difficult labor, birth injuries, meningo-encephalitis or any other exogeneous causes. Neither was there any indication of Rh-incompatibility being involved, insofar as no individual had suffered from hemolytic disease. Nor did the

analysis of the distribution of the patients on different birth ranks favour such an explanation.

Consequently, it was considered probable that the etiology of this syndrome had to be traced back to early fetal life. The neurology and psychiatry suggested symmetric brain lesions, mainly of the frontal lobes and areas 4 and 6 of the cerebral cortex, due to developmental defects. It remained to be tested with whether this defect could be due to a major gene difference.

Distribution on birth ranks.

The result of this calculation (cf. *Böök* and *Rayner* [1950] p. 79) is shown in table 14. The distribution was random, as one would expect for a genetic defect. Of the total of 24 individuals, five were first-born and two last-born.

Table 14. Oligophrenia spastica. Analysis of distribution on different birth ranks. There were 5 first-borns and 2 last-borns.

Birth rank	Observed o	Calculated c	$(o-c)^2/c$
1– 3	10	9.93	0.00
4– 6	7	7.34	0.02
7–12	7	6.69	0.01
Totals	24	23.96	0.03

Chi-square = 0.03; DF = 2 $0.99 > P > 0.98$

Genetic analysis.

The total of 24 individuals belonged to 16 sibships. Fifteen of these sibships could be joined into a connective pedigree (see figure 1). The parents were related as 2:2 in two families, as 2:3 in two, as 3 : 3 in two, as 4:4 inone, and no relationship was disclosed in eight families. In five of these eight families, however, both parents were related to other sibships with affected members.

The type of ascertainment of these affected individuals justifies the use of the *a priori* method of calculation. A test of simple recessive inheritance showed fairly good agreement between the observed and calculated figures (cf. table 15). All parents of the examined sibships were of normal mentality with the exception of sibship no. 218/49, where the mother was schizophrenic. The differences between the affected individuals and their siblings were, with one exception, clearcut. In sibship no. 266/49 no. 3, a male, had been

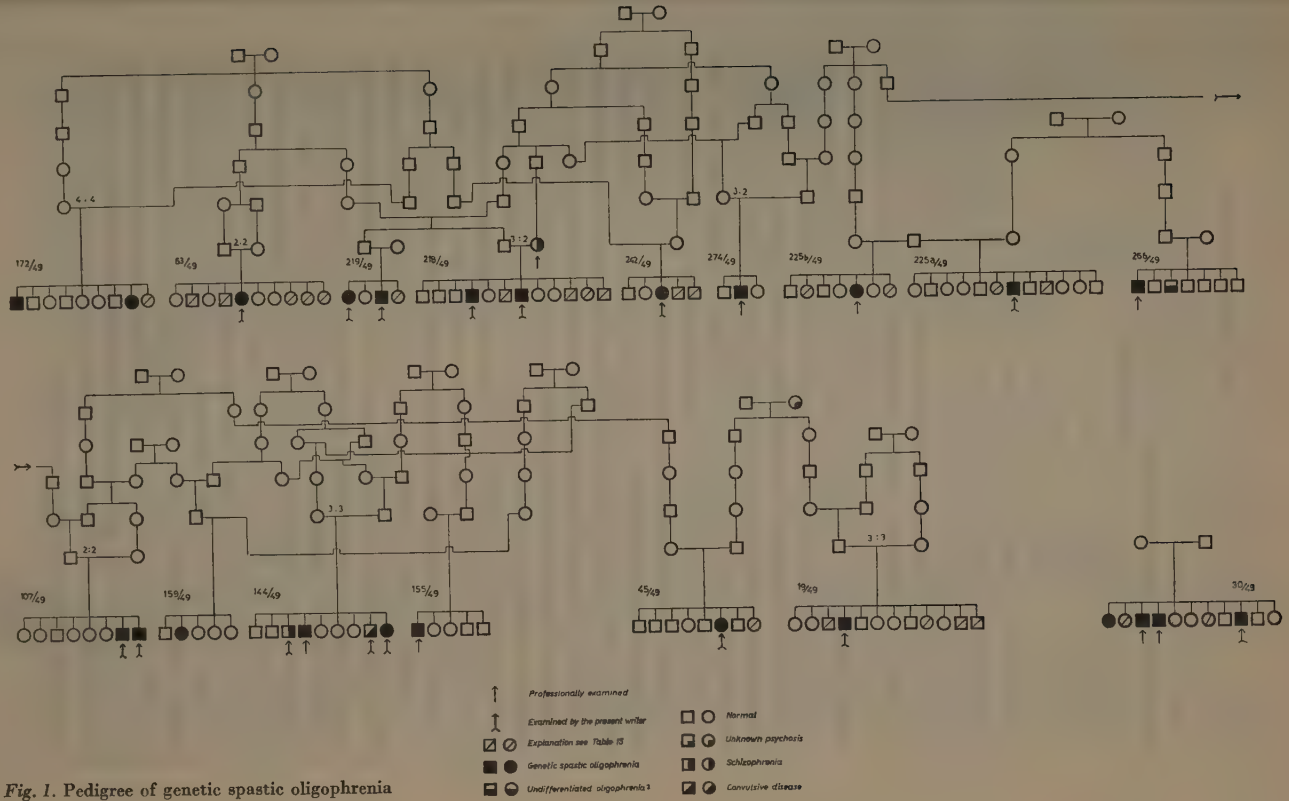


Fig. 1. Pedigree of genetic spastic oligophrenia

Table 15. Oligophrenia spastica. Simple recessive test according to the percentage affected method (*Bernstein-Macklin*). All cases ascertained during 1902–49 have been included.

No. of children per family	Total no. of children	Affected		Not affected		$\Sigma (o-c)^2/c$
		o	c	o	c	
3– 5	29	8	10.45	21	18.55	0.898
7– 8	46	9	12.89	37	33.11	1.631
9–10	29	7	7.73	22	21.27	0.094
Totals	104[1]	24	31.07	80	72.93	2.623

DF = 3 Chi-square = 2.623 $0.30 < P < 0.50$.

[1] Individuals over-crossed in the pedigree (fig. 1) were excluded. These were either stillborn, had died in infancy or early childhood or, though living and below school age, were of unknown status.

diagnosed as mentally deficient by the superintendent of the Welfare Organization. No positive neurologic findings were mentioned in the file. I had no opportunity to examine this individual, who was not included as affected in the calculations.

It was concluded that the individuals described here belonged to a specific clinical and genetic entity caused by a simple recessive gene difference. This condition was named genetic spastic oligophrenia. The similarities between this genetic disease and the one described by *Hanhart* [1936] are apparent, although it cannot be decided if they would be identical. At any rate, it has been shown beyond any doubt that specific genetic entities occur within the heterogeneous group of cerebral palsy. Furthermore, genetic spastic oligophrenia represents another identified specific type of inherited mental defect.

On September 1, 1949, a total of 99 individuals with the main or additional diagnosis of oligophrenia were living and resident in the area. Of these, 13 carried the specific diagnosis of genetic spastic oligophrenia. When calculating the morbid risk of this condition, i.e., the incidence at birth, it is necessary to account for excess mortality. The eleven cases who had died prior to the cross-section day had experienced an average life duration of only 12.9 years. The morbid risk was estimated in three different ways. Due to the very appreciable excess mortality, the incidence in the youngest age group should come closer to the true risk than if all cases were put in relation to their corresponding age groups in the population. The number of individuals and the number of those affected per age group 0–4 years were during the following years:

Year	affected	total
1920	2	791
1930	1	910
1940	5	1,187
1949	1	1,347
Totals	9	4,235

The estimated morbid risk thus would be 9/4,235, or 2.3 per 1,000.

The first known case was born in 1906 and the last in 1947. During the period of 1906–1947, a total of 9,140 births was registered in the area and of these, 24 were affected. The morbid risk estimated on this basis would be 2.6 per 1,000.

On the cross-section day, the crude incidence of genetic spastic oligophrenia was 1.4 per 1,000. None of the cases was above 45 years of age so that the morbid risk might be estimated roughly by taking the population between 0 and 44 years of age into consideration. This will give a figure of 1.8 per 1,000.

If we adopt the morbid risk figure of 2 per 1,000 as a fairly adequate estimate, this would imply a heterozygote frequency of approximately 9 per cent. A correction for the influence of non-random cousin marriages according to *Dahlberg* [1948] (p. 61) does not affect the estimate of the gene frequency (r). Directly one obtains $r = 0.045$ and, with correction, $r = 0.044$. The frequency of first-cousin marriages within the investigation area was 2.2 ± 0.4 per cent.

Due to the thorough investigation of this population also from the point of view of inbreeding conditions, we have the unique possibility of performing a few other calculations based on actual data. All families (i. e., parent-sibship combinations) in which the parents were first cousins and both partners were alive in 1947, were examined (cf. *Böök* [1948]). Details of this study will be published separately later.

In 1947, there was a total of 1,315 marriages with both partners alive in the area. Of these, 29 were between first cousins. On the basis of the estimated heterozygote frequency of 9 per cent, one would expect 8.1 per 1,000 of the 1,286 marriages between non first cousins, i.e., about 10, to be between two heterozygotes. Actually, there were 10 such marriages in which there was at least one child with genetic spastic oligophrenia. Among the remaining 29 cousin marriages, two had issued affected children. The expectancy of two married first cousins both being heterozygotes would be 0.09×0.209[1], or about

[1] i.e. $P = \overline{DR}/8\ (1 + 15r)$ where $\overline{DR}$ is the frequency of heterozygotes.

2 per cent. The observed figure, therefore, is a little too high but could still be due to chance. Under given circumstances, the probability of 2 out of 29 cousin marriages is a little more than 9 per cent. Thus, the observations do not disagree with the genetic explanations given above or with the assumption of the applicability of the *Hardy-Weinberg* law. It is granted that the expected incidence of matings between heterozygotes includes such marriages in which, due to chance, no affected children would appear. By making a comparison as above, this error would have been appreciable in a population with one- or two-child families. In this population, the number of children per family (6–10) is so large that, in case both parents are heterozygous in regard to a simple recessive disorder with complete penetrance, the probability that no affected child will be issued is much reduced (to between 20 and a few per cent). Another source of error is that among the 1,315 marriages were included some of short duration which therefore produced few or no children. In spite of the errors involved, the estimates made here should be acceptable.

Another item of interest would be to test the significance of first-cousin marriages for the occurrence of a relatively rare recessive defect. I am aware of no other study where the incidence of a specific genetic disorder was known in the population as well as among the offspring of all cousin marriages of that particular population. The 29 first cousin marriages had issued a total of 218 children of whom 3 were affected. The remaining 21 cases of genetic spastic oligophrenia, as mentioned above, could be considered as belonging to 9,140 births. The morbid risk of genetic spastic oligophrenia thus was found to be significantly higher among the children of first cousin parents (Chi-square test with *Yate*'s correction gave a value of 15.9 with one degree of freedom; $P < 0.001$).

This result is entirely in agreement with the behaviour of rare simple recessive disorders as anticipated in previous theoretical calculations of population genetics (cf. *Dahlberg* [1929, 1938 and 1947] and others). Consanguineous marriages tend to increase the birth of affected individuals through matings from a more concentrated smaller pool of heterozygotes. It is of practical interest to note that, insofar as the period of 1902–1949 was concerned, the prohibition of first cousin marriages would probably have prevented the births of 3 cases afflicted with genetic spastic oligophrenia in this area. The actual gain thus would have been slight. However, the actual

effect of cousin marriages cannot be dealt with by considering just one particular genetic disorder. This whole problem with regard to this population will be taken up in a following report, now under preparation.

CHAPTER II.

CONVULSIVE DISORDERS

By convulsive disorder is meant, in this study, the occurrence of grand mal seizures. All individuals with such seizures have been registered irrespective of the simultaneous occurrence of other neuropsychiatric disorders. I prefer not to use the term "epilepsy" for two main reasons. It should not be used in medical practice because of its strong emotional attachments whereby it often inflicts a psychologic trauma on the patient and counteracts therapy. From a scientific point of view, it should not be used because it gives the false impression of being a specific disease. The term "convulsive disorder" stresses better the fact that we are concerned with a pattern of brain neuronal discharge, the cause of which is largely unknown.

Alström [1950] recently published a critical review of the literature in regard to convulsive disorders, making a repetition here quite unnecessary. It has been stressed throughout the present paper that genetic analyses can be profitable only if we can work with data which are at least reasonably homogeneous from a biological viewpoint. To that effect, we need much better information than is now available about the specific conditions underlying the symptom, convulsive disorder. Until then, it does not seem likely that genetics can contribute much of substantial value in regard to the etiology of cerebral convulsions. One must also admit that all genetic interpretations that have been offered have been based on inefficient data and consequently remain speculations. The concept, especially of German investigators (*Conrad* [1935] and others), that there is an "idiopathic hereditary epilepsy" which could be diagnosed by exclusive measures remains at least very doubtful.

On the other hand, a number of genetic studies (*Alström* [1950] and others) have provided important information about the incidence of convulsive disorders in the population and among the relatives of selected *propositi*. Taken for what they are, namely empiric risk

figures, they have great value in connection with different public health measures, but they cannot yet be used as a basis of genetic interpretations. In the present study it was not possible to materialize anything beyond this. However, as much work was directed towards the ascertainment of all individuals of the living population who were or had been suffering from convulsive disorder and since I have been convinced that the registration was rather complete, the results might prove useful.

Diagnosis and classification.

The diagnosis of convulsive disorder was, insofar as all living individuals were concerned, based on a history of repeated grand mal attacks. For 7 of those individuals who had died or emigrated by September 1, 1949, the only available information was their registration as "epileptics" in the parish registers. None of them had been institutionalized.

For the period of 1902–1949, a total of 58 individuals with convulsive disorders was registered (cf. table 7 and 8, *Böök* [1953 c]). Of these, 24 had a main diagnosis of oligophrenia (17) or schizophrenia (7). On the cross-section date, 35 individuals were living, of whom 21 had no other diagnoses and thus might be considered as belonging

Table 16. Convulsive disorders. Age distribution of all individuals (living and resident on September 1, 1949) who had had grand mal seizures but carried no other neuropsychiatric diagnosis.

Age	Males	Females
0– 4		
5– 9	1	
10–14	1	2
15–19	1	
20–24	2	1
25–29	2	2
30–34	2	
35–39		
40–44		1
45–49		
50–54	1	1
55–59		1
60–64		
65–ω	3	
Totals	13	8

to the group of *convulsive disorders proper*. Their age distribution is shown in table 16. Of these 21 individuals, 18 were personally examined. The other 3 had been examined and diagnosed by competent neuropsychiatrists. In regard to 19 individuals, no indications of a specific etiology were found. The history of one individual, a woman 22 years of age, strongly suggested meningo-encephalitis as the cause of her disease. She was hospitalized in 1943 under this diagnosis and developed her first seizures two years later, at the age of 17. Another case, a boy of 12 with pronounced personality changes and disorderly conduct, was said to have developed his disease after encephalitis at the age of 7.

Severity of symptoms and custodial care.

Of the 21 individuals mentioned above, 6 had been subjected to custodial care at various times prior to the cross-section date. On September 1, 1949, only one was hospitalized, and 15 had never been under such care, although some of them had been admitted to medical or neurologic clinics for short periods. It should also be mentioned here that only 11 of these individuals had been registered in the parish registers. The remainder were discovered during the field work.

Table 17. Convulsive disorders proper. Cross-sectional *propositi*. Status in regard to personality and presence of seizures on September 1, 1949.

	Age							Total
	Below 10	10–19	20–29	30–39	40–49	50–59	65–ω	
None or only slight personality changes	1	3	3	2[1]	2		3[2]	14
Severe personality changes		2	3			2[3]		7

[1] One individual had had no seizures during the last 10 years.
[2] Three individuals had had no seizures during the last 10 years.
[3] One individual was completely psychotic.

Table 17 gives a summary of the severity of the disease as measured by the extent to which psychopathologic personality changes were observed. As such changes, I specifically included perseverations and affective lability in terms of so-called explosiveness. Those 14 individuals who displayed none or only slight changes displayed no particular difficulties in social accommodation. The remainder (7) had to be judged as being in need of close super-

vision or custodial care. *This would mean that approximately one per 1,000 of the population would need hospitalization in a special institution.*

Marriage and reproduction.

According to an old Swedish law of 1757, those "who suffer from epilepsy originating mainly from endogeneous causes" are forbidden to marry. Although the present data are extremely scanty, it should be of some interest to see how many individuals had married. Taking the women above 16 and the men above 18 years of age, there are 16 such persons and of these, 4 had married. Of 16 exactly comparable random controls, 7 were married.

The same 16 individuals with convulsive disorders had 46 children, or 2.9 children per individual. Exactly the same average was found for 32 comparable controls (in this case one female and one male control for each affected). The figures include children born in as well as out of wedlock. The extramatrimonial reproduction, however, was low for both groups (0.5 and 0.2 children per individual, respectively). Only 6 of the affected individuals had any children at all as compared to 22 out of the 32 controls.

Incidence and general morbid risk.

The crude incidence of all ascertained types of convulsive disorders per September 1, 1949, was for males 21/4,791 = 0.44 $\pm$ 0.10 per cent, for females 14/4,190 = 0.33 $\pm$ 0.09 per cent and for both sexes 35/8,941 = 0.39 $\pm$ 0.07 per cent. For convulsive disorders proper, the corresponding figures were 13/4,791 = 0.27 $\pm$ 0.07 per cent, 8/4,190 = 0.19 $\pm$ 0.07 per cent and 21/8,981 = 0.23 $\pm$ 0.05 per cent.

The morbid risk figures, as calculated on the basis of the weights used by *Alström* (1950, table 17, p. 112), were for males 21/2,114 = 0.99 $\pm$ 0.22 per cent, for females 14/2,004 = 0.70 $\pm$ 0.19 per cent and for both sexes 0.85 $\pm$ 0.14 per cent. In regard to convulsive disorders proper, the corresponding risk were 0.61 $\pm$ 0.17 per cent, 0.39 $\pm$ 0.14 per cent and 0.51 $\pm$ 0.11 per cent.

If one calculates the morbid risk according to *Weinberg*'s abridged method, somewhat lower figures are obtained. For comparison with other studies, the figures in regard to convulsive disease proper will be given here.

	Risk period	Morbid risk, per cent
Males	0–30	13/3,255=0.40±0.11
	10–30	13/2,588=0.50±0.14
Females	0–30	8/2,820=0.28±0.10
	10–30	8/2,168=0.37±0.13
Both sexes	0–30	21/6,075=0.35±0.08
	10–30	21/4,755=0.44±0.10

Previous investigations.

The ascertainment of individuals with convulsive disorders is liable to meet with considerable difficulties, mostly because this illness is still so much feared by the public. This difficulty is apt to be especially pronounced in census studies. Although I had a thorough knowledge of the present population and experienced magnificent cooperation in regard to other neuropsychiatric disorders, I felt a good deal of resentment as soon as convulsive disorders were under discussion. In several cases, the information we had obtained from other sources was completely denied when the family concerned was interviewed. Only after we had interviewed neighbours or other people in the village who were no close relatives and then returned, would the family admit that there might have occurred some occasional seizures. It thus often took a good deal of diplomacy until finally, in most instances, one had the confidence of the patient and his relatives.

Consequently, it is not surprising that the results of previous census studies have varied. Generally, much lower figures than those obtained here have been calculated (cf. *Fremming* [1947], table 3, p. 36–37). The estimated crude incidence averages 0.14 per cent against 0.23 per cent in this study. It seems most probable that the differences are due to a more complete ascertainment in the present population. One of the most complete studies was made by *Fox* [1939] (*op. cit. Fremming* [1947]) of an English population of about 100,000. He calculated a crude incidence of 0.24 per cent, which is practically the same as here. *Anderson* [1936] found 0.21 per cent for a population of 73,000 in Michigan, USA. Other American investigators have found still higher figures, as *Pollock* [1931] 0.51 per cent among American draftees during World War One and *Hodskin* [1939] (*op. cit.*

Fremming [1947]) 0.40 per cent in Massachusetts, USA. According to *Dahlberg* [1937], p. 38, 0.2 per cent of Swedish draftees during 1923–32 were exempted on account of "epilepsy".

Insofar as the general morbid risk is concerned, the only available figures for Sweden are those of *Sjögren* [1935 and 1948]. In two North Swedish isolates he found 0.05 per cent, and in the West Swedish population 0.03–0.04 per cent. As these risk were calculated according to *Weinberg*'s abridged method, they should be compared with my figures of 0.3–0.4 per cent. The differences are, no doubt, due to the fact that *Sjögren* included only those individuals who had been officially reported and/or had been hospitalized. Besides, he observed a very strong tendency to conceal convulsive disorders in the West Swedish population. My general morbid risk figures, on the other hand, agree closely with those of *Fremming* [1947] who used the birth register test. Using *Weinberg*'s abridged method and a risk period of 0–30 years, he obtained for males a risk of 0.30 $\pm$ 0.12 per cent, for females 0.41 $\pm$ 0.15 per cent and for both sexes 0.35 $\pm$ 0.09 per cent.

In summary it might be concluded that the crude incidence of convulsive disorders proper in this population was 0.23 $\pm$ 0.05 per cent and the general morbid risk between 0.3 and 0.5 per cent. A sligh but not significant preponderance of males was noted. It is probably also justified to conclude that the incidence of convulsive disorders in this population does not deviate from that of other so-called general populations.

Parents and siblings.

The parents of the 21 *propositi* were related as 2:2 (one family), 2:3 (one family), 3:3 (two families) and 4:4 (one family). The general incidence of first cousin marriages in the area being 2.21 per cent (2:2), these findings do not indicate increased consanguinity. One of the parents was also a *propositus*, and his parents could not be investigated. Two sibships had two affected members. In one of them the two affected individuals were monozygotic twins. Thus, there are 36 parents recorded, of whom 15 had died and 21 were living. There was one individual with convulsive disease and one with involutional psychosis among the 36 parents.

The morbidity among the siblings has been summarized in table 18. In regard to convulsive disease proper there are only 3

Table 18. Convulsive disorders proper. Calculation of morbid risk for siblings according to *Weinberg*'s method.

Age group	Disappeared from observation as normal	Convulsive disease	Other neuropsychiatric diagnoses	Living and normal	Total without convulsive disease	Corrected rates of reference[1]
0– 4				9	25	0.85
5– 9		1		10	10	1.22
10–14			1[2]	14	15	3.44
15–19	3	1		10	13	4.90
20–24	5		1[2]	3	9	4.48
25–29			1[3]	8	9	5.30
30–34	3			6	9	6.03
35–39	1			6	7	5.28
40–44		1	1[4]	1	2	1.64
45–49	1		1[5]	4	6	5.26
50–54	1		1[6]	2	4	3.73
55–59				1	1	0.97
60–64	1			3	4	3.94
65–ω			1[4]	4	5	4.98
Totals	31	3	7	81	119	52.02

Morbid Risk = 3/55.02 = 5.5 $\pm$ 3.1 per cent.

[1] Corrected rates according to *Alström* [1950]. [2] Genetic spastic oligophrenia. [3] Schizophrenia? [4] Schizophrenia. [5] Unknown psychosis. [6] Oligophrenia.

experiences among the sibs which gave a morbid risk of 5.5 $\pm$ 3.1 per cent. If instead *Alström*'s weights are used for this calculation, one obtains an almost identical figure. Although numerically higher than the general morbid risk of 0.5 $\pm$ 0.1 per cent, the difference is not significant. For the calculations of table 18, I have counted the monozygotic twins as one *propositus*. Only one sibship with two *propositi* was counted twice. Subtracting the double counts, we have in this table a total of 109 *individuals*. Of these, 71 had no history of neuropsychiatric trouble.

The occurrence of neuropsychiatric diagnoses other than convulsive disorders is indicated in table 18. Due to the small number of individuals, it is not possible to say with certainty whether or not the accumulation of these other neuropsychiatric subjects among the sibs is accidental.

The analysis of the convulsive disorders in the present population thus has not given any indications that they (or part of them) would

represent a more homogeneous sample than those of other populations. In this respect the result was disappointing, although not unexpectedly so. The scarcity of the family data and the rather insignificant risks which were calculated for the siblings cannot be used for further genetic penetrations. However, as we have here an unconditioned representative sample of individuals with convulsive disorders, it might be worth while to note that in agreement with *Alström* [1950], I did not find a significantly higher incidence of convulsive disorders among the siblings. It can thus be stated that the trait "convulsive disorder" in this population is too undifferentiated to justify genetic analyses.

SUMMARY AND CONCLUSIONS

This is a summary of 3 papers, published in the "*Acta Genetica et Statistica Medica*" (Karger/Basle):

1. Entitled as above, Part I. Psychoses, Vol. 4 : 1–100 : 1953.
2. Schizophrenia as a Gene Mutation, Vol. 4 : 133–139 : 1953.
3. Entitled as above, Part II. Mental Deficiency and Convulsive Disorders, Vol. 4 : 345–394 : 1953.

i.

The basic consideration which inspired this project was to utilize an isolate for a combined clinical and genetic investigation of *major* neuropsychiatric disorders. An anticipated greater genetic homogeneity of such a population should further the differentiation of specific clinical and genetic entities. This is in agreement with the present theories and, insofar as man is concerned, rather limited, practical experiences of the genetics of populations and isolates. A further objective was to analyse the morbid risks of various neuropsychiatric disorders occurring in this population. I planned and started the project in 1946. The major part of the field work was carried out in 1949 and the final genealogic and statistic data were collected in 1952.

ii.

The investigation area was located in the extreme north of Sweden, some 100 km. north of the Arctic Circle. It comprised the

parishes of Pajala, Junosuando and Muonionalusta. The area, mainly forest and boglands, was 4,875 sq. km. Insofar as the collection of the neuropsychiatric material was concerned, the time covered by this work was 1902–1949. The year 1902 was chosen as a starting point because the Swedish law concerning the official registration of individuals afflicted with insanity, mental deficiency and epilepsy came into effect on January 1, 1902. The population of the investigation area was 4,584 in 1900 and 8,981 in 1949. The population of 1949 very likely consisted mostly of descendants of people who migrated into the area from about 1650 to 1730. The increase of the population from 1900 to 1949 was mainly due to an excess of births. The average fertility was estimated at twice that of the average Swedish rural population.

The investigation area had a pronounced rural character. About 70 per cent of the family supporters were small farmers and/or lumbermen. Communications had been very poor until the 1920's and there were still in 1953 no railways within the area. The general mobility of the population, as measured by crude migration rates had been rather low. The incidence of marriages between first cousins among all marriages existing in 1947 was 2.2 ± 0.4 per cent. The general character of the investigation area thus agreed with the concept of an isolate as this term is used in population genetics.

iii.

The registration of *propositi* for this investigation had the main objective of securing a complete ascertainment of all individuals who were or had been afflicted with major neuropsychiatric disorders and who were living and resident on the census day. The period for registration of *propositi* was 1902–1949. The census analysis referred to September 1, 1949. Individuals registered as *propositi* in this investigation have been ascertained through personal studies of the parish registers, the admission lists of those hospitals which receive neuropsychiatric patients from the area and of the reports of the medical officers delivered to the Swedish Medical Board. This registration of officially known cases was completed by a screening of the living population by means of personal interviews and visits to every part of the area during 1946 to 1949.

iv.

A total of 364 individuals, primarily known as insane, mentally defective or epileptic, were registered. Their genealogies have been

investigated independently of the clinical field examinations. They belonged to 285 parent-sibship combinations and a total of 10,341 ancestors have been investigated. 240 sibships could be joined into one large pedigree complex which went back to 31 ancestral pairs living about 1700–1750. On the cross-section day 217 of these individuals were living and residents of the area. For these 217 cross-sectional *propositi* the neuropsychiatric condition of the parents and siblings was investigated more closely and as far as possible in combination with personal interviews and examinations. The diagnostic work by and large followed the current principles of Scandinavian psychiatry. All available files of individuals admitted to different mental institutions and other hospitals were examined by me, photographed and filed at the State Institute for Human Genetics, Uppsala. Insofar as the diagnoses are concerned, certain qualifications must, of course, be made especially in regard to individuals who had died prior to the beginning of the field work.

V.

The general morbid risks for the different investigated conditions have been summarized in tables 19 and 20. Unless specified, "morbid risk" implies the probability that an individual who outlives the manifestation period of a certain disease will actually get this particular disease. In regard to congenital disorders the morbid risk is equal to an estimate of the incidence at birth. The total risk of *psychoses* was estimated at approximately 3–4 per cent and the total risk of all investigated major neuropsychiatric disorders at about 5 per cent. Most remarkable is the substantial morbid risk (and incidence) of schizophrenia in this population (about 3 times as high as has previously been estimated for so-called general populations). Likewise interesting is the low risk (and incidence) of manic-depressive psychosis. To anticipate a criticism that these findings could be explained on the basis of some peculiarities of the diagnostic principles used in this investigation I want to mention that of the 85 schizophrenics in table 19 no less than 65 had been diagnosed by other physicians as schizophrenias prior to my examination. For a further 5 hospitalized individuals there was enough reason to change the diagnosis from manic-depressive psychosis (3 patients) or from psychogenic psychosis (2 patients) to schizophrenia. Of the remaining 15 individuals 7 had been declared insane by other physicians. Only 8 individuals had never before contacted a physician and were also

officially unknown. A definite explanation of the high prevalence rate of schizophrenia, absolutely and *versus* manic-depressive psychosis, cannot be given but the hypothesis that it would be due to a different composition of this population insofar as specific major gene differences are concerned is supported by a number of facts.

vi.

Schizophrenia. 120 cases were available for an analysis of the symptomatology. The findings indicated rather pronounced similarities between the different individuals and catatonic features dominated. In regard to body type athletics were probably over-represented in this sample. The age of onset was 26.8 ± 1.0 years for males and 29.7 ± 1.5 years for females. The mortality of the schizophrenics after the onset of the disease was estimated at about twice that of the general population. Among the causes of death tuberculosis predominated. Of the 85 cross-sectional *propositi* 35 were in a mental hospital, 21 were cared for at home but in need of hospitalization, 22 were more or less improved but in need of some psychiatric supervision, 7 had recovered and were able to work, 75 were between 20 and 65 years of age.

An analysis of marriage and reproduction rates indicated that the schizophrenic disease as such did not interfere with fecundity. The marriage rate of schizophrenic males was very low which, together with the insignificant number of children born out of wedlock, had the effect that the propagation capacity of the group was somewhat reduced as compared to the average population. The reproductive fitness was estimated at about 70 per cent.

The crude incidence was for males 1.04 ± 0.15 per cent and for females 0.84 ± 0.14 per cent. The general morbid risk was calculated according to 2 different methods:

Method	Morbid risk, per cent	
	Males	Females
Weinberg's abridged method (risk period 15–45 years)	2.22 ± 0.33	2.62 ± 0.41
Dahlberg-Stenberg-Schulz	2.47 ± 0.37	2.97 ± 0.47

With correction for excess mortality the general morbid risk of schizophrenia in this area was estimated at approximately 3 per cent.

As the series of observational data was unconditionally representative the genetic enumerations of the individuals and sibships were made according to *Weinberg*'s method.

The morbid risk for parents of schizophrenic *propositi* was 12.0±2.7 per cent (according to *Weinberg*'s abridged method and a risk period of 15–50 years).

The morbid risks for siblings were:

Method	Morbid risk, per cent		
	Two non-schizophrenic parents	One schizophrenic parent	Two schizophrenic parents
Weinberg's abridged method (risk period 15–45 years)	8.5±1.8	11.6±4.1	(60.0)
Dahlberg-Stenberg-Schulz .	9.1±1.9	12.5±4.4	

The figure of 60 per cent above was based on one single family and is thus by itself of no great value but a statistical calculation showed that the accumulation in this family was significantly higher than for the other combinations ($P = 0.004$). All the above risks were significantly higher than the general morbid risk in this population. As a basis for the genetic analysis I adopted the following estimates of the morbid risks: population 3 per cent, parents 12 per cent, siblings of *propositi* of two non-schizophrenic parents 9 per cent, and siblings of *propositi* of one schizophrenic and one non-schizophrenic parent 12 per cent. The incidence of first cousin marriages among the parents of the *propositi* was not significantly increased. The distribution of the schizophrenic individuals on different birth ranks was random.

The available data were best interpreted by the hypothesis that the type of schizophrenia prevalent in the investigation area was due *primarily* to a major simple dominant gene with a heterozygous penetrance of about 20 per cent and a homozygous penetrance of about 100 per cent. The frequency of the gene in the population was estimated at about 7 per cent. The penetrance refers to a schizophrenic psychosis as defined in the paper.

As there was a definite selection against schizophrenia it was reasonable to assume that some cases should be due to new mutations. In the paper "Schizophrenia as a Gene Mutation", which is rather speculative, I have discussed some important possibilities in regard to the mutational origin of schizophrenia. If the premises are correct the findings would indicate a mutation frequency of 5×10^{-3} genes per generation. This would also imply that 6–7 per cent of the schizophrenics would be new mutations, a suggestion of considerable

importance for further investigation. Due regard has been paid to other explanations of the etiology of schizophrenia but it was concluded that, insofar as the basic mechanism is concerned, environmental (psychodynamic) hypotheses rest on substantially less reliable and much more scanty factual data than does the genetic explanation.

vii.

In regard to other psychoses the data allowed only estimates of the general morbid risk. These have been summarized in tables 19 and 20.

viii.

The diagnosis of *oligophrenia* (mental deficiency) was based on clinical and social considerations. The individuals included in this investigation were roughly equivalent to those having an upper IQ limit of 60–70. By using a combined clinical and genetic analysis an attempt was made to differentiate specific types of oligophrenia.

In regard to *all types of oligophrenia* the reproductive capacity was found to be rather low. According to the Swedish law marriage is prohibited for oligophrenics but a few individuals had married. The mortality was considerably increased, although an accurate figure could not be calculated. The crude incidence of oligophrenia was 1.21 ± 0.16 per cent for males, 0.98 ± 0.15 per cent for females and 1.10 ± 0.11 per cent for both sexes. The general morbid risk (without correction for excess mortality) was 1.28 ± 0.14 per cent (inclusive of individuals with a main diagnosis of a psychosis). In comparison with other population investigations, in which similar criteria were used, the incidence of oligophrenia in this population does not seem to deviate appreciably. About 10 per cent of the oligophrenic individuals appeared to be defective on account of environmental injuries.

The majority displayed no characteristic features (granted that the methods of examination were limited in conformity with what was practically possible during a field study). This *undifferentiated group* had a crude incidence of 0.75 ± 0.09 per cent. An analysis of the families of such undifferentiated oligophrenic *propositi* was made according to standard methods. The morbid risks of oligophrenia was 4.1 ± 2.0 per cent for parents and 9.7 ± 1.9 per cent for siblings. The latter figure was significantly higher than the general risk in this population.

About 10 per cent of all living oligophrenics were *mongoloid idiots or imbeciles*. The crude prevalence rate was 1.1 per 1,000. The

general morbid risk was calculated at 0.25–0.50 per cent (i.e. of all births). Age specific morbid risks were calculated at 0.06 per cent for mothers between 18 and 40 years of age and at 2.1 per cent for mothers 40 years of age or above. The hypothesis of a mutational origin of mongolism was discussed briefly.

Among the oligophrenics of this population a specific clinical and genetic entity could be differentiated, called *genetic spastic oligophrenia.* This was a congenital and stationary condition characterized by symmetric spastic motor defects predominantly of the legs combined with severe mental defect. Altogether 24 cases were available for analysis and of these 13 were cross-sectional *propositi.* The general morbid risk was estimated at about 2 per 1,000 births. The average duration of life was about 13 years. The selection against the trait was complete. A genetic analysis showed good agreement with a hypothesis of a simple recessive gene difference. The total consanguinity between the parents was raised and the 24 cases belonged to 16 sibships which all, except one, could be joined into one connective pedigree. The results left no reasonable doubt that, within the heterogeneous group of cerebral palsies, there exist specific genetic types, although they are presumably not common in ordinary samples.

ix.

It was stressed that individuals displaying *convulsive disorders* (grand mal) seem to belong to a biologically heterogeneous group. The clinical and genetic analysis of the data from this population did not contribute to a nosologic differentiation. However, the thorough investigation of the living population admitted estimates of the incidence of convulsive disorders which should be adequate. Including all individuals who had or previously had had grand mal seizures (i.e., also those with a main diagnosis of oligophrenia or schizophrenia) the prevalence rate per September 1, 1949 was for males 0.44 ± 0.10 per cent, for females 0.33 ± 0.09 per cent and for both sexes 0.39 ± 0.07 per cent. The general morbid risk figures were 0.99 ± 0.22 per cent, 0.70 ± 0.19 per cent and 0.85 ± 0.14 per cent respectively.

In regard to *convulsive disorders proper* the prevalence rates were for males 0.27 ± 0.07 per cent, for females 0.19 ± 0.07 per cent and for both sexes 0.23 ± 0.05 per cent. The general morbid risks according to *Weinberg's* abridged method (risk period 0–30 years) were for males 0.40 ± 0.11 per cent, for females 0.28 ± 0.10 per cent and for both sexes 0.35 ± 0.08 per cent. These figures are in close agreement with

those previously reported as valid for the general population of Denmark. There was thus no reason to assume that the incidence of convulsive disorders in this population was outstanding.

The morbid risk for siblings, irrespective of parental combination was 5.5±3.1 per cent and thus not significantly different from the general morbid risk of this population.

Table 19. Morbid risks of major neuropsychiatric disorders for the population of the parishes of Pajala, Junosuando and Muonionalusta, Sweden. Cross-section examination per September 1, 1949. Population 8,981.

Disorder	No. of cases alive Sept. 1, 1949 and then residents	Risk period or age limit	Corrected rates of reference	Morbid risk[1], per cent
Schizophrenia	85	20–40	3,236	2.63±0.28
		20–45	3,023	2.81±0.30
		15–45	3,410	2.49±0.27
		15–50	3,234	2.63±0.27
Manic-depressive psychosis	2	15–65	2,849	0.07±0.05
Senile or involutional psychosis	4	50	1,224	0.33±0.16
		60	653	0.61±0.30
Convulsive disease proper	21	0–30	6,070	0.35±0.08
		10–30	4,749	0.44±0.10
Oligophrenia, all types	72[2]	10	6,340	1.14±0.13

[1] No corrections for excess mortality have been made in this table.

[2] In addition there were 9 cases with a main diagnosis of schizophrenia or involutional psychosis If these are included the morbid risk will be 1.28±0.14 per cent. Only oligophrenics above 10 years of age were included.

Table 20. Some further morbid risks of specified neuropsychiatric disorders for the population of the parishes of Pajala, Junosuando and Muonionalusta, Sweden.

Disorder	No. of cases alive Sept. 1, 1949 and then residents	Risk period or age limit	Corrected rates of reference	Morbid risk, per cent
Psychosis during pregnancy or puerperium	3	15–45	1,545	0.19±0.11
Oligophrenia of probable environmental origin	7	10	6,340	0.11±0.04
Mongolism[1]	(13)		(5,231)	0.25±0.07
Genetic spastic oligophrenia[1]	(24)		(9,140)	0.26±0.05

[1] These calculations do not belong to the census examination but refer to the number of births shown in column 3.

RÉSUMÉ

RECHERCHES D'ORDRE GÉNÉTIQUE ET NEUROPSYCHIATRIQUE EFFECTUÉES DANS UNE POPULATION DU NORD DE LA SUÈDE

en tenant surtout compte des cas de schizophrénie et d'imbécillité.

Ce résumé concerne 3 articles publiés dans «*Acta Genetica et Statistica Medica*» (Karger/Basel), notamment:

1. Même titre que ci-dessus, 1e partie. Psychoses. Vol. 4:1–100:1953.
2. Schizophrénie due à une mutation du gène. Vol. 4:133–139:1953.
3. Même titre que ci-dessus, 2e partie. Imbécillité et maladies convulsives. Vol. 4:345–394:1953.

1.

Comme point de départ général pour ces recherches, on a utilisé un isolat géographique permettant d'effectuer une analyse combinée, à la fois clinique et génétique, des maladies et défauts neuropsychiatriques de nature grave. Un isolat (voir la génétique de la population) doit être plus homogène du point de vue génétique que d'autres populations moins sédentaires. Cette homogénéité doit également s'appliquer, dans une certaine mesure, aux maladies et défauts génétiques qui se rencontrent dans l'isolat. D'autre part, on a examiné la morbidité et les risques de contracter la maladie relatifs aux différents états pathologiques du groupe en question. Les recherches se sont poursuivies de 1946 à 1952.

2.

Le domaine des recherches s'est étendu aux paroisses de Pajala, Junosuando et Muonionalusta, dans le département de Norrbotten, en Suède. Il s'agit d'une région de caractère rural nettement prononcé, située à environ 100 km. au nord du cercle polaire, à la frontière finlandaise. Le nombre d'habitants s'élevait, en 1900, à 4.584, et en 1949, à 8.981.

3.

L'enregistrement des cas princeps avait essentiellement pour but la mise sur pied d'un inventaire complet de tous les cas (y compris les cas de guérison) existant dans la région le jour du recensement, le 1er septembre 1949. Cet enregistrement comprenait la période allant

de 1902 à 1949 et était basé sur des enquêtes faites dans les registres paroissiaux, dans les rapports des médecins de province et dans les archives des hôpitaux ayant abrité les malades de la région. Pour compléter ces renseignements, on a entrepris, entre 1946 et 1949, une série de recherches personnelles très poussées dans toutes les parties du domaine d'investigation, ce qui a permis de découvrir un nombre important de cas nouveaux.

4.

On a enregistré un total de 364 cas princeps pour la période comprise entre 1902 et 1949. Une enquête généalogique approfondie a été menée parallèlement. Ces cas princeps appartenaient à 285 fratries. 10 341 généalogies ont été établies en tout. 240 fratries se sont révélées comme appartenant au même groupe de parenté, lequel était issu de 31 ancêtres vivant aux environs de 1700–1750. 217 cas princeps étaient en vie le jour du recensement, dont on a examiné personnellement, pour autant que possible, également les parents et les frères et sœurs. On a étudié les fiches de toutes les personnes ayant séjourné à l'hôpital. Le diagnostic a été posé pour la majeure partie selon la nomenclature psychiatrique habituelle en Scandinavie.

5.

Les risques de morbidité pour les différents défauts et maladies examinés ont été groupés sur les tableaux 19 et 20. Jusqu'à nouvel avis, le risque de morbidité équivaut, pour un individu qui traverse toute la période de manifestation d'une maladie, à la probabilité de réellement contracter cette maladie. En ce qui concerne les défauts congénitaux, le risque de morbidité équivaut à la fréquence de cette anomalie chez les nouveaux-nés.

Le risque total de psychoses est estimé à 3 ou 4 % et le risque total pour toutes les maladies et défauts psychiques examinés est d'environ 5 %.

Le résultat qui nous a paru le plus remarquable a été le risque (et la fréquence) considérable de schizophrénie dans cette population, environ 3 fois plus élevé que les résultats obtenus lors des recherches précédentes, effectuées sur d'autres populations. Par contre, les psychoses maniaco-dépressives se sont révélées très rares. On n'a pas pu donner d'explication tout à fait satisfaisante de ce phénomène. La plus probable cependant serait qu'il dépend de la structure génétique propre à ce groupe.

6.

Schizophrénie.

La symptomatologie s'est révélée assez homogène, avec dominance des traits catatoniques. L'âge de manifestation est de 26,8±1,0 ans pour les hommes et de 29,7±1,5 ans pour les femmes. Aucune diminution de la fertilité n'a pu être enregistrée, mais le taux de reproduction est estimé à environ 70 % seulement, ce qui résulte principalement de la fréquence peu élevée des mariages chez les hommes schizophréniques. La fréquence non corrigée de la schizophrénie (y compris les cas de guérison) s'élevait, le jour du recensement, à 0,95±0,10 %. Le risque général de morbidité, compte tenu de la surmortalité, était évalué à 3 %. Le risque d'être affectés était estmié à 12,0±2,7 % pour les parents des cas princeps schizophréniques, à 9,1±1,9 % pour les frères et sœurs dont aucun des parents n'était schizophrénique, et à 12,5±4,4 % pour les frères et sœurs dont un des parents était schizophrénique. L'analyse génétique montrait que les chiffres obtenus s'expliquaient de la façon la plus satisfaisante par l'hypothèse selon laquelle la forme de schizophrénie examinée ici dépend principalement d'un gène dominant qui, sous une forme hétérozygote, se manifeste à environ 20 % et, sous une forme homozygote, à environ 100 %. On a tenu compte des facteurs du milieu ambiant et des autres hypothèses concernant l'étiologie de la schizophrénie. La possibilité que la schizophrénie dépende d'un gène labile ayant un taux de mutation élevé, est discutée.

7.

Oligophrénie.

Ce diagnostic s'applique à une catégorie allant des imbéciles proprement dits, jusqu'à ceux dont le niveau d'intelligence correspond à un quotient de 60–70. La fréquence non corrigée des cas d'oligophrénie s'élevait, le jour du recensement, à 1,10±0,11 %. Le risque général de morbidité était (sans tenir compte de la surmortalité) de 1,28± 0,14 %. On pouvait considérer qu'environ 10 % des cas d'oligophrénie étaient dus à l'influence de facteurs exogènes. En ce qui concerne les cas princeps oligophrènes de type non différencié, on estime que le risque de morbidité s'élève, pour les parents, à 4,1±2,0 % et, pour les frères et sœurs, à 9,7±1,9 %.

Environ 10 % des oligophrènes étaient des *idiots mongoliens*. Le risque général de morbidité était évalué, pour cette forme, de 0,25 à 0,50 %.

On a pu déterminer une forme spéciale d'oligophrénie héréditaire appelée *oligophrénie spastique génétique*. Il s'agissait d'un état stationnaire et congénital, caractérisé par des troubles moteurs spastiques et symétriques atteignant surtout les extrémités inférieures, et lié à un état d'oligophrénie grave. 24 cas en tout ont pu être analysés et, sur ceux-ci, 13 étaient en vie le jour du recensement. L'analyse génétique a montré que, selon toute probabilité, il était question d'une simple hérédité récessive. La fréquence de cette maladie chez les nouveaux-nés était d'environ 2 pour 1000.

8.

Le risque général de morbidité a été évalué, en ce qui concerne l'épilepsie (sans rapport avec l'oligophrénie ou la psychose), à $0{,}35 \pm 0{,}08\,\%$. Le risque de morbidité pour les frères et sœurs des cas princeps atteints de telles maladies était de $5{,}5 \pm 3{,}1\,\%$. Aucun indice ne laisse supposer que des formes génétiques spécifiques d'épilepsie se soient manifestées parmi cette population.

ZUSAMMENFASSUNG

EINE GENETISCHE UND NEUROPSYCHIATRISCHE UNTERSUCHUNG IN EINER NORDSCHWEDISCHEN BEVÖLKERUNG

Im besonderen Hinblick auf Schizophrenie und Oligophrenie.

Die Zusammenfassung bezieht sich auf drei in «*Acta Genetica et Statistica Medica*» (Karger, Basel) veröffentlichte Aufsätze, und zwar:

1. Titel wie oben, Teil 1, Psychosen; Band 4:1–100:1953.
2. Schizophrenie als Genmutation; Band 4:133–139:1953.
3. Titel wie oben, Teil 2, Oligophrenie und Epilepsie; Band 4:345–394:1953.

I.

Es war der allgemeine Ausgangspunkt der Untersuchung, ein geographisches Isolat zu einer kombinierten klinischen und genetischen Analyse der sogenannten schwereren neuropsychiatrischen Krnakheiten und Defekte auszunutzen. Man kann nämlich anneh-

men, daß ein Isolat aus dem Gesichtspunkt der Genetik homogener ist als andere in höherem Grad bewegliche Populationen. Diese Homogenität wird in gewissem Umfang auch für genetische Krankheiten und Defekte innerhalb des Isolates gelten müssen. Eine weitere Aufgabe bestand darin, die Morbidität und das Erkrankungsrisiko für verschiedene der genannten Gruppe zugehörende Krankheitszustände zu untersuchen. Die Untersuchung fand statt von 1946 bis 1952.

II.

Das Untersuchungsgebiet bestand aus den Gemeinden Pajala, Junosuando und Muonionalusta, Regierungsbezirk Norrbotten, in Schweden. Es handelt sich um ein ausgeprägt ländliches Gebiet ungefähr 100 km nördlich vom Polarkreis an der finnischen Grenze. Die Einwohnerzahl war schon im Jahre 1900 4 584 und im Jahre 1940 8 981.

III.

Die Registrierung von Probanden hatte hauptsächlich den Zweck, alle Fälle einschließlich Genesungsfälle, die am Stichtag, dem 1. September 1949, im Gebiet ihren Wohnsitz hatten, vollständig zu inventieren. Die Registrierung umfaßte die Zeit von 1902 bis 1949 und gründete sich auf Nachforschungen in den Kirchenbüchern, in den Berichten der Amtsärzte und in den Journalarchiven der Krankenhäuser, die Patienten des Gebietes aufnehmen. Ergänzend wurden von 1946 bis 1949 umfassende eigene Felduntersuchungen in allen Teilen des Gebietes vorgenommen, wobei mehrere neue Fälle angetroffen wurden.

IV.

Alles in allem wurden für die Jahre 1902 bis 1949 364 Probanden registriert. Parallel damit wurde eine vollständige genealogische Untersuchung durchgeführt. Die Probanden gehörten zu 285 Geschwistergruppen. Insgesamt erfaßte die Untersuchung 10 341 Vorfahren. 240 Geschwistergruppen gehörten zum gleichen Familienkomplex, der auf 31 Vorfahrenpaare, die zwischen 1700 und 1750 lebten, zurückzuführen war. Am Stichtag lebten 217 Probanden. Für diese Stichtagsprobanden wurden Nachforschungen über alle Eltern und Geschwister angestellt, soweit möglich in Verbindung mit eigenen Untersuchungen des Verfassers. Bezüglich aller Personen, die im Krankenhaus waren oder gewesen waren, wurden die Originaljournale nachgeprüft. Die Diagnose wurde im großen ganzen entsprechend der Praxis der skandinavischen Psychiatrie gestellt.

V.

Das allgemeine Erkrankungsrisiko für verschiedene untersuchte Krankheiten und Defekte ist in den Tabellen 19 und 20 zusammengestellt. Soweit nichts anderes gesagt ist, bedeutet «Erkrankungsrisiko» die Wahrscheinlichkeit dafür, daß ein Individuum, das die ganze Manifestationsperiode einer gewissen Krankheit erlebt, tatsächlich von dieser Krankheit befallen wird. In Bezug auf angeborene Defekte ist das Erkrankungsrisiko gleich der Häufigkeit des Auftretens des fraglichen Defektes bei Neugeborenen.

Das totale Psychosenrisiko wurde auf 3–4 Prozent und das totale Risiko für alle untersuchten psychischen Krankheiten und Defekte auf wenigstens 5 Prozent geschätzt. Besonders auffällig war das bedeutende Risiko (und die hohe Frequenz) für Schizophrenie, die in dieser Population das Resultat früherer Populationsuntersuchungen mit etwa dem Dreifachen übertraf. Gleichzeitig erwiesen sich manisch-depressive Psychosen als äußerst selten. Eine erschöpfende Erklärung dieser Erscheinungen kann nicht gegeben werden. Die Ursache ist jedoch wahrscheinlich in der speziellen genetischen Struktur der Bevölkerung zu suchen.

VI.

Schizophrenie. Die Symptomatologie erwies sich als ziemlich einheitlich, wobei katatone Züge dominierten. Das Erkrankungsalter war $26{,}8 \pm 1{,}0$ Jahre für Männer und $29{,}7 \pm 1{,}5$ für Frauen. Eine Herabsetzung der biologischen Fruchtbarkeit war nicht festzustellen. Die totale Reproduktion betrug jedoch schätzungsweise nur ungefähr 70 Prozent, hauptsächlich infolge der geringen Ehefrequenz bei schizophrenen Männern. Für Schizophrenie mit Einschluß der Genesungsfälle war am Stichtag die unkorrigierte Frequenz $0{,}95 \pm 0{,}10$ Prozent. Unter Berücksichtigung der Übersterblichkeit war der Schätzungswert für das allgemeine Erkrankungsrisiko 3 Prozent. Das Erkrankungsrisiko für die Eltern von schizophrenen Probanden wurde auf $12{,}0 \pm 2{,}7$ Prozent berechnet, das für Geschwister mit zwei nicht-schizophrenen Elternteilen auf $9{,}1 \pm 1{,}9$ Prozent und für Geschwister mit einem schizophrenen Elternteil auf $12{,}5 \pm 4{,}4$ Prozent. Die genetische Analyse der erhaltenen Werte macht es wahrscheinlich, daß die hier untersuchte Schizophrenieform *primär* auf einem dominanten Gen beruht, das in heterozygotischer Form mit etwa 20 Prozent und in homozygotischer Form mit etwa 100 Prozent manifest wird. Bei der Untersuchung wurde auf Umweltsfaktoren

Rücksicht genommen, und es wurde auch anderen Hypothesen über die Ätiologie der Schizophrenie in Betracht gezogen. Die Möglichkeit wird erörtert, daß die Schizophrenie auf ein labiles Gen mit hoher Mutationsfrequenz zurückzuführen ist.

VII.

Oligophrenie. Der Begriff umfaßt die eigentlichen Schwachsinnigen bis zu Personen mit einer Intelligenzentwicklung entsprechend einer Intelligenzquote von 60 bis 70. Für Oligophrenie war am Stichtag die unkorrigierte Frequenz $1{,}10 \pm 0{,}11$ Prozent. Das allgemeine Erkrankungsrisiko (ohne Berücksichtigung der Übersterblichkeit) war $1{,}28 \pm 0{,}14$ Prozent. Etwa 10 Prozent der Schwachsinnigen wurden als infolge von Umweltsschäden defekt beurteilt. Bei den schwachsinnigen Probanden nicht-differenzierten Typs wurde das Erkrankungsrisiko der Eltern auf $4{,}1 \pm 2{,}0$ Prozent und der Geschwister auf $9{,}7 \pm 1{,}9$ Prozent berechnet.

Etwa 10 Prozent der Schwachsinnigen waren *mongoloide Idioten.* Das allgemeine Erkrankungsrisiko dieser Form wurde auf 0,25–0,50 berechnet.

Eine spezielle Form von erblich bedingtem Schwachsinn war zu unterscheiden und wurde als *genetische spastische Oligophrenie* bezeichnet. Es handelt sich hierbei um einen angeborenen stationären Zustand, gekennzeichnet durch symmetrische, spastische motorische Störungen, hauptsächlich an den unteren Extremitäten, kombiniert mit hochgradigem Schwachsinn. Alles in allem waren 24 Fälle zur Beurteilung verfügbar und von diesen lebten am Stichtag 13. Die genetische Analyse ergab, daß es sich mit größter Wahrscheinlichkeit um einfach rezessive Vererbung handelt. Das allgemeine Erkrankungsrisiko wurde auf etwa 2 pro 1000 Neugeborene berechnet.

VIII.

Das allgemeine Erkrankungsrisiko für Epilepsie (ohne Zusammenhang mit Schwachsinn oder Psychose) wurde auf $0{,}35 \pm 0{,}08$ Prozent berechnet. Das Erkrankungsrisiko für die Geschwister von Probanden mit dieser Diagnose war $5{,}5 \pm 3{,}1$ Prozent. Es ergaben sich keine Anhaltspunkte dafür, daß innerhalb dieser Population spezielle genetische Formen von Epilepsie vorkämen.

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From the Institute of Genetics, University of Lund, Sweden
(Head: Professor Arne Müntzing, Ph.D.)

GARBER'S TOE DEFORMITY

Report on a kindred

By CARL A. LARSON

A toe deformity which was first described by *Garber* [1950] as an inherited trait has been observed in three consecutive generations of the Swedish family O in which the mother of the eldest living member was also said to have had the anomaly. The proband, a normal woman, was observed by chance to have this toe deformity.

II:2 was a 65 year old woman with hallux valgus on both feet. The second toe on both feet partly overlay the distal ends of the first and the third toes. On the left foot the distal end of the fourth

toe deviated in tibial direction and partly covered the distal phalanx of the third toe. On the radiograms no skeletal abnormalities were observed.

III:3, the proband, was a 33 year old woman with hallux valgus and digitus V varus on both feet. On the left foot the end phalanx of the second toe was pressed down between the hallux and the overlapping third toe. On the radiograms no skeletal abnormalities were observed.

IV:5 was a 3 year old girl who had slightly elevated second toes on both feet, more easily discernible on the right foot. The distal end of the second toe rested partly on the first and the third toes. Radiograms of both feet showed that the distal phalanx of the second toe was somewhat thick. When re-examined two years later the second

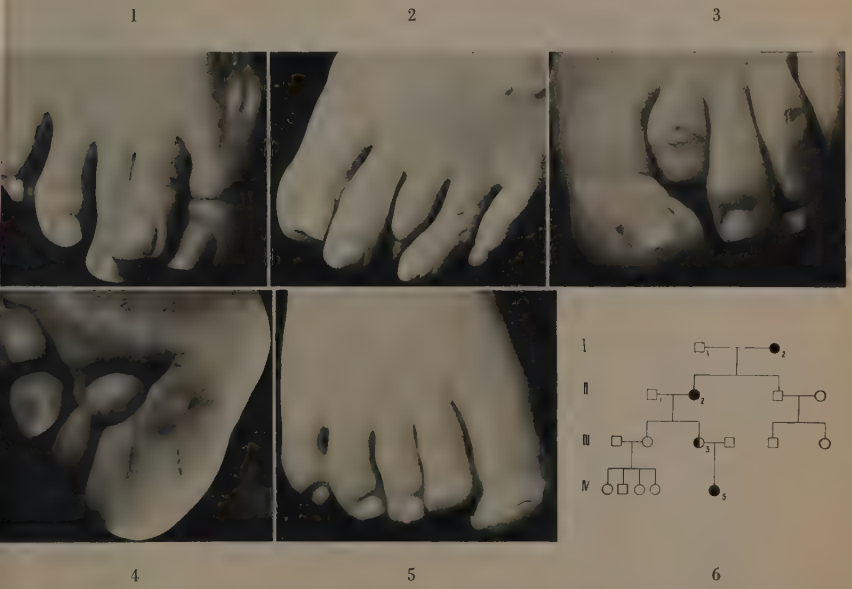

Fig. 1. Right foot of II:2. – *Fig. 2.* Left foot of II:2. – *Fig. 3.* Left foot of III:3, dorsal view. – *Fig. 4.* Left foot of III:3, plantar view. – *Fig. 5.* Right foot of IV:5. – *Fig. 6.* Pedigree chart showing incidence of *Garber*'s toe deformity in the 0 family. Half-filled circle denotes one-sided manifestation, filled circle bilateral. I:1, I:2 and II:1 died before the investigation was begun. All others were examined by the author.

toe exhibited the same slight tendency to overlie the first and the third toes.

The inheritance of this anomaly could be dominant with variable expressivity as *Garber* suggests. The sex distribution observed in the O pedigree can occur by chance and, therefore, is not contrary to *Garbers* assumption of an autosomal gene.

Summary.

In a Swedish family a toe deformity occurred in four consecutive generations. It was variably expressed as a deviation of the second and, sometimes, even other toes in tibial-fibular and dorso-plantar direction. The deformity could be present in one or both feet. It is identified with the abnormality described by *Garber* as a dominant trait with variable expression.

Résumé.

Une déformation des orteils apparaît dans une famille suédoise dans quatre générations consécutives. Elle se manifeste sous une forme variable par une déviation du deuxième, et parfois même des autres orteils, dans une direction tibia-péroné et dorso-plantaire. Cette déformation se présentait à un pied ou aux deux. Elle s'identifie avec celle décrite par *Garber* comme un caractère dominant avec expression variable.

Zusammenfassung.

In einer schwedischen Familie kam eine Zehendeformität vor in vier konsekutiven Generationen. Sie manifestierte sich variierend als eine Deviation der zweiten und in einigen Fällen mehrere Zehen in tibial-fibuläre und dorso-plantare Richtung. Die Deformität konnte in einem Fuß oder in beiden manifestiert sein. Diese Deformität ist identisch mit einer von *Garber* beschriebenen Zehenanomalie, die dominant vererbt ist und sich variabel manifestiert.

I should like to thank Docent *Olof Norman*, M.D., pro tempore head of the Roentgen Diagnostic Department, University Hospital of Lund, for the radiologic examination.

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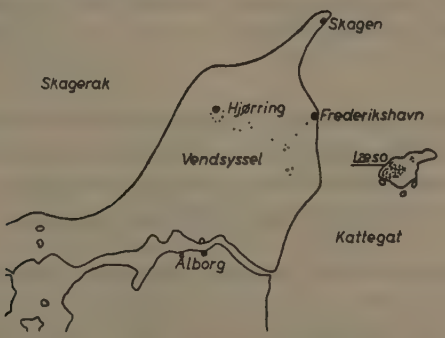
Nørholm, A. and *N. B. Nielsen*: Acta genet. 4, 417–423, 1953

From the Clinic of Dermatology, University of Copenhagen
(Director: Professor H. Haxthausen, M. D.)
and the Institute of Human Genetics, University of Copenhagen
(Director: Professor Tage Kemp, M. D.)

"LAESØ DISEASE" – EPIDERMOLYSIS BULLOSA SIMPLEX

By A. NØRHOLM-PEDERSEN and N. BIRCH NIELSEN

For some generations eruptions of bullae involving the hands and feet have been observed in certain families on the island of Læsø and in the western regions of Vendsyssel. One of these families has previously been described in detail by *Bartels* [1939]; it then comprised 55 members of which 25, 11 males and 14 females, were affected with epidermolysis. *Bartels* was successful in tracing the parentela to Læsø whereto the latter had probably immigrated. Later investigators (*Bülow* and *Nørholm-Pedersen* [1953]) have demonstrated similar cases on Læsø where, for several generations, the complaint has been called "Læsø Disease".



Map of the northern part of Jutland.

The island of Læsø comprises an area of 113 sq. kilometres with 3,400 inhabitants (1945) living mainly by fishery. The dots indicate the localization of the cases of epidermolysis.

Aetiology.

Epidermolysis bullosa occurs in many different forms, accounted for by a variety of clinical and hereditary factors, but based on the presence of a number of common characteristics the disease may be divided into the two main groups which *Siemens* [1921, 1923, 1935] named: epidermolysis bullosa recessiva-dystrofica and epidermolysis bullosa dominans-simplex. The simple type includes a few cases of irregular dominance (*Gottron* [1929]) and another few cases apparently due to mutation (*Cockayne* [1933]). Deviations from the chiefly recessive mode of inheritance of the dystrophic type are more frequent, however. The following occurrences seem probable: dominant forms (*Hoffmann* [1926]), irregular, dominant forms (*Bülow* and *Nørholm-Pedersen*), and several cases in which mutation cannot be ruled out (*Bülow* and *Nørholm-Pedersen* [1953]).

Morphologically the simple forms present a rather uniform picture, characterized by bullae affecting the hands and/or feet, distinct seasonal variations and, in very rare cases (about 2 per cent), lesions of the mucous membranes. The dystrophic form, on the other hand, comprises a number of highly varying pictures, accounted for by differences in time of onset, morphological characteristics and course. The most well-defined sub-groups are the following: (1) the frustraneous form (*Hallopeau* [1898], *Riecke* [1931]), (2) the vegetating form (*Nicolas*, *Moutot* and *Charlet* [1913], *Brain* [1952]) and (3) the lethal form (*Jenny* [1927], *Herlitz* [1936]) – varieties which prognostically and morphologically represent degrees ranging from mild, transitory cases to fatal cases and cases of universal extension.

Frequency and occurrence of epidermolysis in Denmark.

In 1952 (*Bülow* and *Nørholm-Pedersen*), a rough estimate was made of the various forms of epidermolysis occurring in Denmark, their principal findings of the investigation are summarized in the following:

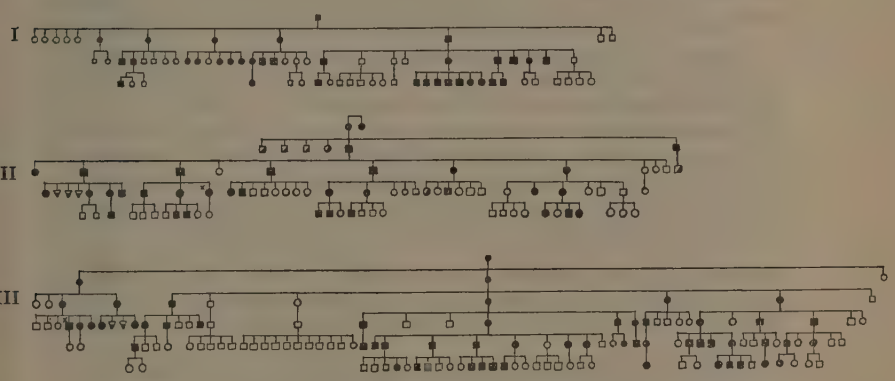
Epidermolysis bullosa simplex was found in 96 members of 10 families totalling 286 persons. In 9 of the families the condition was dominant, whereas mutation was most likely in the tenth. 5 of the 10 families could be traced to Læsø.

Epidermolysis bullosa dystrophica was encountered in 31 instances occurring in 11 families totalling 200 members. In 6 families the disease was apparently recessive, but owing to the small number

of children it was not possible to rule out mutation. In one family it was dominant, and in the remaining four (excepting one, in which there was a probability of mutation) there was a recessive inheritance. The geographical distribution of the disease was casual. In several cases the prognosis was favourable so far as both recovery (spontaneous) and life were concerned, in others it was poor in regard to both.

Epidermolysis bullosa letalis was demonstrated in 9 cases distributed over 3 families totalling 67 members. In addition to these cases there had been two infant deaths from congenital malformation. The disease was recessive in two of the families and irregularly dominant in the third. The geographical distribution of cases was casual.

Epidermolysis bullosa (*frustraneous form*) was found in 4 cases distributed over 3 families totalling 59 members. The condition was recessive in one family, in the remaining two there was a probability of either recessiveness or mutation. The geographical distribution was casual and the prognosis favourable.



Family I ● ■ ▼ epidermolysis bullosa simplex.
○ □ ▽ woman, man, sex unknown without ep. bull.
Family II ◕ ◪ ▽ morbidity unknown.

Authors' study.

The present study comprised 3 families. Family I, the family recorded by *Bartels* [1939], had been augmented by a number of members in the past 14 years. Families II and III were inhabitants of Læsø.

Family I. The family lived in the neighbourhood of Hjørring (Vendsyssel) and, as mentioned earlier in this paper, the parentela had conveyed the disease to that part of the country from Læsø. The pedigree comprised 72 individuals, 34 females and 38 males. The number of epidermolysis patients, their sibs and descendants was 60. 34 of these, 15 females and 19 males, were affected with the disease. Conductors were 7 females and 5 males. There was no intermarriage of blood relations and no sex-limited inheritance. In the fourth generation there was a pair of twins, one, a boy, was affected, the other, a girl, was healthy.

Viewed from the eugenic standpoint the distribution of the disease to other parts of the country was regarded as being of considerable interest. In the second generation one affected member was living outside Vendsyssel (Copenhagen) and had normal children. Two members of the third generation were living in Copenhagen, one had no offspring, the other had normal children. Two members of the fourth generation were living outside Vendsyssel, one at Holstebro had two children with epidermolysis, the other at Sebbersund had 7 children with the disease.

All the affected members presented a uniform morphological picture, characterized by bullae localized to the hands and/or feet, considerable aggravation of the condition in summer (i.e. in warm weather) and improvement of or freedom from bullae in winter. None gave a history of lesions of mucous membranes. The disease had persisted without change in two women aged 66 and 61 respectively and in one man aged 48. A man aged 37 had experienced some improvement of the disease at the age of 30. In the younger members the condition remained unchanged.

Family II. The family included 85 persons, 43 females, 39 males and 3 of unstated sex (emigrated to the U.S.A.). The number of epidermolysis patients, their sibs and descendants was 73. 35 of these, 18 females and 17 males were affected. The disease had been transmitted by 10 females and 6 males. As no information was available on the presence of symptoms in 2 females and 4 males (also emigrated to the U.S.A.) and on the sex and clinical manifestations in another 3, it was not possible to dermine the relative share of the sexes in the frequency of epidermolysis. There were no marriages between blood relations and no sex-limited inheritance.

All the family members, down to and including the third generation, were inhabitants of Laesø. In the fourth generation one lived at Ribe and had a son with epidermolysis, one in Copenhagen had two boys with the defect, another one in Copenhagen had no offspring, and one at Birkerød had two girls and one boy with the disease.

The morphological features were identical with those reported for Family I.

In the young age groups the disease persisted without change, whereas persons aged 37, 82, 55 and 76, respectively, stated that they had experienced some improvement. None gave a history of affection of the mucous membranes.

Family III. Information was available on 135 persons, 59 females, 74 males and 2 in which sex and manifestations were unknown. Epidermolysis patients, their sibs and descendants numbered 114. 56 of these, 28 females and 28 males were affected. 15 females and 11 males had transmitted the disease. So far there had been no occurrence of epidermolysis amongst the children of 5 affected persons in the second-youngest generation having a maximum offspring of 2.

In regard to the distribution of the disease to other parts of the country the findings were as follows: One member of the fourth generation lived at Odense and had one boy with epidermolysis, another one in Copenhagen had no offspring. One affected member of the fifth generation lived at Oddesund and had 3 boys with the defect.

Detailed information on the course of the disease was available in 23 cases. One patient had his first bullae at the age of 21 when he was receiving military training, in all the others the first eruptions of bullae occurred before the age of 2. All the patients experienced an aggravation of bullae in summer. In one the disease disappeared at the age of 30, in 7 others there had been some improvement later in life, between the ages of 50 and 70, and in the remainder, mostly of the younger age groups, the disease had remained unchanged.

Discussion.

Viewed as a whole, the three families presented a stereotype picture in regard to morphology and prognosis. The disease developed within the two first years of life and persisted with severe eruptions of bullae in summer and mild symptoms or freedom from symptoms in winter. There was only one instance (in Family III) in which the first symptoms occurred at a later time of life, and the disease disappeared completely in only one patient. There was no occurrence of other anomalies in the three families.

Family	No. of sibs among which epidermolysis bullosa occurred	No. affected	Distribution by sex ● ■		Conductors ● ■		Unknown ▽	◐	◪
I	60	34	15	19	7	5			
II	73	35	18	17	10	6	3	2	4
III	114	56	28	28	15	11	2		
Total	247	125	61	64	32	22	5	2	4

The disease was found to be typically dominant and of equally frequent occurrence in both sexes, which is in agreement with the observations of *Siemens*, but female conductors appeared to be in excess of male conductors. Contrary to observations in patients with the dystrophic form there was no intermarriage of blood relations; this point has recently been stressed by *Noojin*, *Reynolds* and *Croom* [1952], and supports the view that simple epidermolysis occurs by mutation.

As regards the inconveniences attending epidermolysis bullosa it is worth mentioning that most affected persons had been able to

settle in occupations making fairly heavy demands on manual work, and few gave a history of change of occupation. Military service, on the other hand, produced traumatic injury of the feet of a severity making it impossible for the sufferers to complete their period of service. Persons with epidermolysis must therefore be considered unfit for any kind of military service.

There was a moderate distribution of the disease to other parts of the country. Viewed against the background of the favourable prognosis quoad vitam, the poor prognosis quoad sanationem and the absence of other familial anomalies, there is no doubt that there will be a gradual increase in the number of epidermolysis patients in other parts of the country. The non-occurrence of other familial anomalies and the ability of the affected persons to settle down in the various occupations militate against eugenic intervention. However, a sibship in which there is a high incidence of the disease seems to offer a clear indication for such intervention.

Summary.

A presentation is made of 3 families with epidermolysis bullosa (dominant form). One of the families lived in Vendsyssel, the other two on the island of Læsø. The various sibships in which the disease occurred numbered 247 individuals of which 125, 61 females and 64 males, were affected. The disease was transmitted by 32 females and 22 males.

There was no intermarriage of blood relations and no sex-limited inheritance.

The distribution of the disease from the places of origin to other parts of the country was moderate but of considerable interest owing to the favourable prognosis quoad vitam and the absence of other familial anomalies.

Epidermolysis patients are deemed unfit for any kind of military service but eugenic intervention is called for only in sibships in which there is an accumulation of cases.

Résumé.

Description de trois familles atteintes d'épidermolyse bulleuse héréditaire (forme dominante). Une de ces familles demeure à Vendsyssel, les deux autres dans l'île de Læsø.

Les fratries dans lesquelles la maladie fut constatée comprennent

247 personnes dont 125 (61 femmes et 64 hommes) sont atteintes. La maladie est transmise par 32 femmes et 22 hommes. Il n'y a pas de mariages consanguins et la transmission héréditaire n'est pas limitée au sexe.

L'extension de la maladie des lieux d'origine dans d'autres régions du pays a été modérée mais offre un intérêt considérable à cause du pronostic favorable *quoad vitam* et de l'absence d'autres anomalies dans ces familles.

On peut estimer que des personnes atteintes d'épidermolyse sont inaptes au service militaire, mais c'est seulement pour les fratries dans lesquelles il existe une accumulation de cas qu'on doit envisager des mesures eugéniques.

Zusammenfassung.

Das Auftreten der dominanten Form der Epidermolysis bullosa in 3 Familien, deren eine in Vendsyssel, die anderen auf der Insel Læsø ansässig sind, wird beschrieben. Die verschiedenen Sippschaften, in denen die Krankheit auftrat, umfaßte 247 Personen, von denen 125 (61 Frauen und 64 Männer) befallen waren. Die Krankheit wurde 32mal durch Frauen und 22mal durch Männer übertragen. Ehen zwischen Blutsverwandten und geschlechtsbegrenzte Vererbung liegen nicht vor.

Die Ausbreitung der Krankheit von den Herkunftsorten auf andere Teile des Landes war geringfügig, jedoch von Wichtigkeit in bezug auf die günstige Prognose quoad vitam und das Fehlen anderer familiärer Anomalien.

Patienten, die an Epidermolysis leiden, sind untauglich für jede Art von Militärdienst; eugenische Eingriffe werden jedoch nur für notwendig erachtet, wenn innerhalb einer Familie eine Häufung der Krankheitsfälle eintritt.

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